Antidepressants, Other
Therapeutic Class Review (TCR)

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Magellan Rx Management
Attention: Legal Department
6950 Columbia Gateway Drive
Columbia, Maryland 21046

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Major Depressive Disorder (MDD)	Generalized Anxiety Disorder (GAD)	Social Anxiety Disorder (SAD)	Panic Disorder	Other Indications
bupropion HBr* (Aplenzin®)[1]	Valeant/Bausch	X	--	--	--	--
bupropion HCl ER* (Forfivo XL®)[2]	generic†, Almatica	X	--	--	--	--
bupropion HCl ER (Wellbutrin® XL)[3]	generic, Valeant/Bausch	X	--	--	--	prevention of major depressive episodes associated with seasonal affective disorder
bupropion HCl IR[4,5]	generic	X	--	--	--	--
bupropion HCl SR (Wellbutrin® SR)[6]	generic, GlaxoSmithKline	X	--	--	--	--
desvenlafaxine ER base*[7]	Ranbaxy/Sun	X	--	--	--	--
desvenlafaxine succinate ER (Pristiq®)[8]	generic, Wyeth/Pfizer	X	--	--	--	--
duloxetine (Cymbalta®)[9]	generic, Eli Lilly	X	X	--	--	diabetic peripheral neuropathic pain; fibromyalgia; chronic musculoskeletal pain
duloxetine delayed-release* (Drizalma Sprinkle™)[10]	Sun	X	X	--	--	diabetic peripheral neuropathic pain; chronic musculoskeletal pain
esketamine‡ (Spravato®)[11]	Janssen	X treatment-resistant depression (TRD); depressive symptoms with acute suicidal ideation or behavior	--	--	--	--

IR = immediate-release; ER = extended-release; SR = sustained release

* Approved under the abbreviated 505(b)(2) pathway, which allows at least some data for approval to come from studies not conducted by or for the applicant.

† Available as authorized generic

‡ Esketamine (Spravato) is a Schedule III controlled substance. The effectiveness of esketamine in preventing suicide or reducing suicidal death has not been demonstrated; its use does not preclude the need for hospitalization, when clinically needed, regardless of patient symptom improvement following an initial dose. Esketamine is not approved as an anesthetic agent; its safety and efficacy as such has not been demonstrated.

FDA-Approved Indications (continued)

Drug	Manufacturer	Major Depressive Disorder (MDD)	Generalized Anxiety Disorder (GAD)	Social Anxiety Disorder (SAD)	Panic Disorder	Other Indications
isocarboxazid (Marplan®)[12]	Medilink/Validus	X 2nd line therapy	--	--	--	--
levomilnacipran (Fetzima®)[13]	Allergan/Forest	X	--	--	--	--
mirtazapine tablet and ODT (Remeron®; Remeron SolTab)[14]	generic, Merck/Organon	X	--	--	--	--
nefazodone[15]	Teva	X	--	--	--	--
phenelzine (Nardil®)[16]	generic, Pfizer	X 2nd line therapy	--	--	--	--
selegiline (Emsam®)[17]	Mylan Specialty	X	--	--	--	--
tranylcypromine (Parnate®)[18]	generic, Concordia	X 2nd line therapy	--	--	--	--
trazodone[19]	generic	X	--	--	--	--
venlafaxine[20]	generic	X	--	--	--	--
venlafaxine ER capsule (Effexor XR®)[21]	generic, Wyeth/Pfizer	X	X	X	X	--
venlafaxine ER tablet (Venlafaxine ER)[22]	generic, Trigen	X	--	X	--	--
vilazodone HCl (Viibryd®)[23]	Allergan	X	--	--	--	--
vortioxetine (Trintellix®)[24]	Takeda	X	--	--	--	--

IR = immediate-release; ER = extended-release; SR = sustained release

The use of duloxetine (Cymbalta, Drizalma Sprinkle) for the treatment of indications other than depression and anxiety are not addressed in this therapeutic class review.

Sage Therapeutics' brexanolone (Zulresso™) is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression in adults.[25] It is supplied as a 100 mg/20 mL single-dose vial for continuous intravenous (IV) infusion over 60 hours. It must be administered in the presence of a healthcare provider in order to provide continuous monitoring during the infusion. Brexanolone is a Scheduled IV controlled substance and has a Risk Evaluation and Mitigation Strategies (REMS) program to address the risk of serious harm resulting from excessive sedation and sudden loss of consciousness. Due to its administration requirements, it is not detailed in this therapeutic class review.

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OVERVIEW

Depressive Disorders

Major Depressive Disorder (MDD)

In the United States (US) during 2009 to 2012, depression was reported in 7.6% of the population, with a higher prevalence rate in those aged 40 to 59 years and females.[26] The US Preventive Services Task Force (USPSTF) recommends screening for MDD in adolescents ages ≥ 12 years and in adults.[27,28] This should be supplemented with precautions to ensure accurate diagnosis as well as appropriate treatment and follow-up. The evidence for screening in patients < 12 years is insufficient to make a recommendation.

The primary pharmacologic treatment for MDD is an antidepressant.[29] While effectiveness is generally comparable among classes and within classes of antidepressants when analyzed over a large population, the adverse event and safety profiles of the older first generation agents (tricyclic antidepressants [TCAs], oral monoamine oxidase inhibitors [MAOIs]) have greatly reduced their use as first-line agents. The most commonly prescribed antidepressants over the past several years, the selective serotonin reuptake inhibitors (SSRIs), as their name implies, selectively block the reuptake of the neurotransmitter serotonin at the neuronal membrane; these agents are examined in a separate therapeutic class review. The second generation antidepressants, a heterogeneous group of compounds, are now most commonly used as first- and second-line therapy for MDD. Most other second generation antidepressants (non-SSRIs) exert their effects by inhibiting the reuptake and/or blocking the receptors of 1 or more of the neurotransmitters thought to be involved in the etiology of depression – dopamine, norepinephrine, and serotonin. Until recently, known differences among antidepressant drugs were generally limited to safety and tolerability issues. However, over the past handful of years, a number of studies have emerged to evaluate possible differences among antidepressant classes in their ability to resolve specific symptoms of depression when applied at the patient-specific level, related to slight differences in the pharmacologic targets of each agent. Each of the groups of drugs in this class has a potential role in the treatment of MDD, primarily as a result of their heterogeneous spectrums of activity.

With appropriate treatment, 70% to 80% of patients experiencing MDD achieve response.[30] However, as many as one-half of all patients do not experience sufficient symptom improvement with initial treatment. Among patients who remit, residual symptoms are common and associated with impaired psychosocial functioning and increased relapse rates. As with many psychotropic drugs, patients failing to respond to 1 type of antidepressant may respond to a switch to, or augmentation with, an antidepressant with another mechanism of action.

The 2010 American Psychiatric Association (APA) treatment guidelines for patients with MDD recommend an SSRI, SNRI, mirtazapine, and bupropion as appropriate for initial treatment of most patients.[31] Guidelines recommend electroconvulsive therapy (ECT) as the most effective treatment for treatment-resistant depression. Data showing superiority in efficacy in a specific class of drugs (e.g., MAOIs, TCAs, SSRIs, SNRIs, and other antidepressants, including bupropion, nefazodone, trazodone, or mirtazapine) are not robust or clinically meaningful. Each class differs in their adverse event profiles and safety, characteristics that should be considered when choosing an initial therapy. Other factors to

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consider include drug interaction profiles, pharmacokinetics, patient preference, and historical patient response. As these guidelines are more than 5 years old, the APA considers these as legacy guidelines.

The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines on unipolar depression from 2013 and 2015 state the goal of the acute treatment phase is remission, the goal of the continuation treatment phase is relapse prevention, and the goal of maintenance treatment is prevention of both a new episode and suicide.[32,33] Regarding specific treatments, no single class of antidepressants has proven to be more effective or have a more rapid onset than another; however, limited data suggest that select TCAs and venlafaxine may be slightly more effective in severely depressed hospitalized patients. Regardless, treatment selection should be based on several individual patient factors and newer antidepressants and generally tolerated better than older classes (e.g., TCAs, MAOIs). For mild episodes, they suggest non-pharmacotherapy (medication may be considered for patients with past moderate to severe episodes), while they recommend newer antidepressants for moderate and severe depression. TCAs may also be considered for severe depression. They further note that patients will not respond sufficiently to an adequate trial of a first-line therapy in ≥ 30% of episodes. In these cases, strategies for treatment include maximizing the dose, switching to another class or another drug within the class, combination therapy (e.g., multiple drugs or drug plus psychotherapy), augmentation, or other nonpharmacologic therapy (e.g., light therapy, electroconvulsive therapy in select patients). Each strategy should be individualized and has clinical caveats. For maintenance treatment, they recommend continuing treatment for at least 6 to 9 months after remission. Although no clear recommendation is made for treatment beyond that timeframe, which may extend from a few years to a lifetime, they do state that longer-term maintenance therapy is indicated in patients with a history of ≥ 3 episodes or high rate of recurrence.

In 2016, the American College of Physicians (ACP) issued guidelines on the nonpharmacologic and pharmacologic treatment of adult patients with MDD.[34] After a review of the literature, the ACP found that cognitive behavioral therapy (CBT) and second generation antidepressants are similarly effective and have similar discontinuation rates. Treatment with either CBT or second generation antidepressants for MDD is recommended after discussing treatment effects, adverse effects, preferences, and accessibility with the patient. The ACP does not recommend a specific antidepressant over another, but note that bupropion is associated with a lower rate of sexual adverse effects and venlafaxine has a higher rate of nausea and vomiting and discontinuation syndrome (flu-like symptoms, insomnia, imbalance, sensory disturbance, hyperarousal).

Studies of SSRIs were the first to show antidepressant efficacy in children.[35] As a result, SSRIs are used most often for the treatment of children with MDD. The SSRIs are also first-line agents for the treatment of anxiety disorders in children. Non-SSRI antidepressants are most often used as first-line therapy in children in the presence of comorbidities, such as attention-deficit/hyperactivity disorder (ADHD), where bupropion may be more effective than an SSRI. In 2018, the American Academy of Pediatrics (AAP) published part 1 and part 2 of an updated guideline for adolescent depression in primary care (GLAD-PC).[36] Part 1 focuses on practice preparation, identification, assessment, and initial management. Key recommendations within the guidelines include annual screening of patients ≥ 12 years of age and additional attention to the identification of depression in at risk youth, due to prevalence of approximately 20% by 20 years of age. Emphasis is placed on relevant referrals and resources for identified patients, and systematic assessment using reliable depression scales and

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diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5]). Additionally, recommendations were made for completing patient and caregiver interviews and psychoeducation, establishing relevant community links, and the creation of a safety plan. Part 2 recommends direct and continued monitoring of mildly depressed youth, psychotherapy, evidence-based treatment (e.g., CBT, interpersonal therapy for adolescents, antidepressant treatment for youth with moderate to severe depression), collaboration among healthcare providers, close supervision of side effects and outcomes, and specific recommendations for continuation of therapy in those with minimal improvement after start of initial therapy. Notably, the only agent approved for use in patients < 18 years of age in this therapeutic class review is selegiline (Emsam), although select other antidepressants (e.g., some SSRIs) are approved for use in certain patients < 18 years of age.

The North American Menopause Society and National Network on Depression Centers published consensus guidelines for the treatment of perimenopausal depression in 2018.[37] The groups recommend evidence-based treatment with antidepressants, CBT, and other psychotherapies as first-line treatment of major depressive episodes, with treatment selection based on the patient's prior experience with these agents, adverse events, and drug-drug interactions. They note that SSRIs and SNRIs, particularly desvenlafaxine, have been shown to improve menopause-associated symptoms (e.g., vasomotor symptoms, pain, sleep disturbances, night sweats); however, none of the agents in this class are approved for symptoms of menopause.

Treatment-resistant depression (TRD) occurs in approximately 20% to 30% of patients with MDD.[38,39,40] Although there is no official definition, TRD is often defined as a failure of patients to respond after ≥ 2 treatment attempts of adequate dose and duration in a single depressive episode. In 2019, esketamine (Spravato) nasal spray was approved for TRD.[41] Ketamine has been used off-label for several years for this purpose with some data supporting its efficacy; however, standard dosing and approaches have been limited.[42] The exact mechanism by which these N-methyl-D-aspartate (NMDA) receptor antagonists exert their antidepressant effect remains unknown.[43] Although there are no current guidelines specific to TRD, the 2010 APA guidelines state that if there is an adequate response after optimizing the antidepressant dose for an adequate duration of time (e.g., 4 to 8 weeks), switching to another antidepressant (from the same or a different class) and augmentation with another antidepressant from a different class or non-antidepressant medication (e.g., lithium, thyroid hormone, or an atypical antipsychotic/SGA) are recommended subsequent treatment options.[44] In addition to psychotherapy, other nonpharmacologic treatment options include transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), and electroconvulsive therapy (ECT). The APA recommends that ECT should be considered in patients with MDD that is unresponsive to psychotherapeutic and/or pharmacologic treatments. VNS may be appropriate for patients who do not respond to additional antidepressants (≥ 4) and ECT. Efficacy of TMS compared with ECT has been mixed in randomized trials. In addition, the need for daily TMS treatments may present logistical barriers, although it is generally well-tolerated and associated with low rates of treatment dropout. The APA guidelines do not provide recommendations on the role of NMDA antagonists, such as esketamine.

During patient evaluation and ongoing follow-up, providers must monitor patients for suicide risk, which should include inquiries regarding suicidal thoughts, plans, intents, means, and behaviors; specific psychiatric symptoms and medical conditions that may impact the likelihood of a suicide

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attempt; past suicidal ideation and family history of mental illness; currents stressors or protective considerations; and patient support system and independence, among others.[45,46,47] Predictive instruments may be used to supplement a full assessment. This information is used to determine the best treatment setting and strategy to maximize patient safety and clinical benefit. The treatment approach in patients with depressive symptoms with acute suicidal ideation or behavior remains similar, but the APA depression guidelines recommend establishing a therapeutic alliance, close surveillance, and consideration of an increased intensity of treatment (e.g., complete or partial hospitalization, psychotherapy plus pharmacotherapy). Antidepressants are the mainstay of therapy. In select cases of acute suicide risk, ECT also may be considered. Treatment selection may also be impacted by medication safety in an overdose. Additional agents may be used to augment antidepressants but are not approved for depression (e.g., lithium, mood stabilizers) or for the prevention of suicide (e.g., antipsychotics). Like the APA's MDD guidelines, their guidelines on assessment and treatment of patients with suicidal behaviors, published in 2003, are also considered legacy documents. The only agent approved in this class specifically for depressive symptoms with acute suicidal ideation or behavior is esketamine (Spravato); for approval, its use was studied in combination with initial inpatient hospitalization and comprehensive standard of care treatment, including a newly initiated or optimized antidepressant (e.g., antidepressant, antidepressant plus augmentation therapy).

Seasonal Affective Disorder

Seasonal affective disorder is characterized by seasonal changes during the year with recurrent episodes of depression usually in the late fall and winter.[48] The depressive episodes alternate with periods of normal or high mood the rest of the year. Seasonal affective disorder is more commonly diagnosed in women, beginning in their twenties, although men also report seasonal affective disorder of similar severity. People living far north or south of the equator experience seasonal affective disorder more frequently. In Florida, 1% of residents experience seasonal affective disorder compared to 9% living in New England or Alaska. Bright white fluorescent light therapy is now considered the first-line treatment intervention and, if properly dosed, it can produce relief within days.[49] Antidepressants may also help and, if necessary, can be used in conjunction with light.

Anxiety Disorders

Generalized Anxiety Disorder (GAD)

GAD affects about 6.8 million adult Americans and about twice as many women as men.[50,51,52] The disorder develops gradually and can begin across the life cycle, though the risk is highest between childhood and middle age. GAD is diagnosed when a person worries excessively about a variety of everyday problems for at least 6 months.[53,54] People with GAD are unable to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation warrants. Patients cannot relax, startle easily, and have difficulty concentrating. Often, they have trouble falling asleep or staying asleep. Physical symptoms that often accompany the anxiety include fatigue, headaches, muscle tension, muscle aches, difficulty swallowing, trembling, twitching, irritability, sweating, nausea, lightheadedness, having to go to the bathroom frequently, feeling out of breath, and hot flashes. For GAD, the ICGDA recommends SSRIs, SNRIs, TCAs, and CBT as first-line treatments.[55]

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The 2012 WFSBP guidelines recommend SSRIs, SNRIs, and pregabalin as first-line therapies for the treatment of anxiety, obsessive-compulsive, and post-traumatic stress disorders in primary care.[56,57] TCAs are equally effective for some disorders, but many are less well tolerated than the SSRIs and SNRIs. In treatment-resistant cases, benzodiazepines may be used when the patient does not have a history of substance abuse disorders. Although these guidelines focus on medications, non-pharmacological interventions were also considered. CBT and other variants of behavior therapy have been sufficiently investigated in controlled studies in patients with anxiety disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) to support them being recommended either alone or in combination with the above medications. Notably, none of the agents in this class are approved for the use of OCD or PTSD.

Panic Disorder

Panic disorder is a severe, chronic anxiety disorder characterized by recurrent episodes of panic and the development of fear or anxiety regarding the possibility of future panic attacks. Estimates for the incidence of panic disorder range between 2% to 3% of Americans per year, with women being affected twice as much as men. Epidemiologic studies estimate that up to 13.2% of the general population experience isolated panic attacks, whereas up to 12.8% of those experiencing panic attacks met DSM-5 criteria for panic disorder.[58,59,60] The 2009 American Psychiatric Association (APA) treatment guidelines recommend SSRIs, SNRIs, TCAs, and benzodiazepines as first-line pharmacotherapy for panic disorder.[61] The guideline further states that all are roughly comparable in efficacy, but the relatively favorable safety and side effect profile of SSRIs and SNRIs make them the best initial choice for many patients.[62] SSRIs have the largest evidence base for the condition. Benzodiazepines are appropriate as monotherapy only in the absence of a co-occurring mood disorder and may be useful as adjunct to antidepressants to treat residual anxiety symptoms.

Social Anxiety Disorder

In the US, social anxiety disorder affects approximately 12.1% of adults at some point in their lives.[63,64,65] It is the third most common psychiatric disorder after depression and alcohol abuse. This disorder is characterized by a marked and persistent fear of social or performance situations in which embarrassment may occur. Women and men are equally likely to develop the disorder, which usually begins in childhood or early adolescence. There is some evidence that genetic factors are involved. Social anxiety disorder is often accompanied by other anxiety disorders or depression, and substance abuse may develop if people try to self-medicate their anxiety. For social anxiety disorder, the ICGDA expert panel guidelines recommend SSRIs as first-line therapy.[66]

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PHARMACOLOGY[67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100]

Mechanism of Action	TCAs	SSRIs	MAOIs isocarboxazid phenelzine selegiline tranylcypromine	NMDA Inhibitors esketamine	NDRIs bupropion	Norepinephrine-Serotonin Modulators mirtazapine	Serotonin Modulators nefazodone trazodone	Serotonin Reuptake Inhibitor/ Partial Agonists vilazodone vortioxetine	SNRIs duloxetine levomilnacipran venlafaxine desvenlafaxine	Clinical and Physiological Effects
Acetylcholine receptor blockade	Yes	No	No	No	No	No	No	No	No	xerostomia, constipation, sinus tachycardia, memory impairment
Dopamine uptake inhibition	No	No	No	No	*Yes	No	No	No	No	antidepressant efficacy, euphoria, anti-Parkinson's activity, aggravation of psychosis
Histamine-1 receptor blockade	Yes	No	No	No	No	Yes	No	No	No	sedation, antipruritic effect
Monoamine oxidase inhibition	No	No	*Yes	No	No	No	No	No	No	antidepressant efficacy, acute hypertension
N-methyl-D-aspartate inhibition	No	No	No	*Yes	No	No	No	No	No	Dissociative disorder, sedation, dizziness, nausea, increased blood pressure
α_1 Norepinephrine receptor blockade	Yes	No	No	No	No	No	Yes	No	No	orthostatic hypotension, sedation
α_2 Norepinephrine receptor blockade	No	No	No	No	No	*Yes	No	No	No	antidepressant efficacy, sexual effects

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Pharmacology (continued)

Mechanism of Action	TCAs	SSRIs	MAOIs	NMDA Inhibitor	NDRIs	Norepinephrine-Serotonin Modulators	Serotonin Modulators	Serotonin Reuptake Inhibitor/ Partial Agonist	SNRIs	Clinical and Physiological Effects
			isocarboxazid phenelzine selegiline tranylcypromine	esketamine	bupropion	mirtazapine	nefazodone trazodone	vilazodone vortioxetine	duloxetine levomilnacipran venlafaxine desvenlafaxine	
Norepinephrine uptake inhibition	Yes	No	No	No	*Yes	No	No	No	*Yes	antidepressant efficacy, blood pressure, tremors, diaphoresis
Serotonin uptake inhibition	Yes	*Yes	No	No	No	No	*Yes	Yes	*Yes	antidepressant efficacy, nausea, loose stools, insomnia, anorgasmia
Serotonin receptor blockade	No	No	No	No	No	Yes	No	No	No	anti-nausea
Serotonin-2A receptor blockade	Yes	No	No	No	No	*Yes	*Yes	No	No	antidepressant efficacy, REM sleep, anxiolysis, anti-EPS
Serotonin-2C receptor blockade	No	No	No	No	No	*Yes	No	No	No	anxiolytic efficacy, appetite, motor restlessness
Serotonin partial agonist	No	No	No	No	No	No	No	Yes	No	not yet defined

TCA – tricyclic antidepressant, NDRI – norepinephrine dopamine reuptake inhibitor, SNRI – serotonin norepinephrine reuptake inhibitor
*The predominant therapeutic effects of each drug

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PHARMACOKINETICS[101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119, 120,121,122,123,124]

Drug	Protein Binding (%)	Half-Life (hr)	Active Metabolites
bupropion HBr (Aplenzin)	84	21.3	erythrohydrobupion, hydroxybupropion, threohydrobupropion
bupropion HCl (Forfivo XL , Wellbutrin SR, Wellbutrin XL)	84	20 - 21	erythrohydrobupropion, hydroxybupropion, threohydrobupropion (half-lives 20-37 hours)
desvenlafaxine ER base and succinate (desvenlafaxine ER, Pristiq)	30	11	glucuronide metabolite (19%) and N,O-didesmethylvenlafaxine (< 5%)
duloxetine (Cymbalta)	> 90	12	none
duloxetine delayed-release (Drizalma Sprinkle)	> 90	12.4	none
esketamine (Spravato)	43 - 45	7 - 12	none
isocarboxazid (Marplan)	--	--	--
levomilnacipran (Fetzima)	22	12	none
mirtazapine (Remeron, Remeron SolTab)	85	20 - 40	desmethyl metabolite
nefazodone	> 99	11 - 24	hydroxynefazodone, mCPP
phenelzine (Nardil)	--	11.6	none
selegiline (Emsam)	90	18 - 25	none
tranylcypromine (Parnate)	--	--	--
trazodone	--	5 - 9	m-chlorophenylpiperazine, mCPP
venlafaxine tablet	27	5	O-desmethyl-venlafaxine (half-life 11 hours)
venlafaxine ER capsule (Effexor XR)	27	5	O-desmethyl-venlafaxine (half-life 11 hours)
venlafaxine ER tablet (Venlafaxine ER)	27	10.7	O-desmethyl-venlafaxine (half-life 12.5 hours)
vilazodone HCl (Viibryd)	96 – 99	25	none
vortioxetine (Trintellix)	98	66	none

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bupropion (Aplenzin, Forfivo XL, Wellbutrin SR/XL, generic)

The peak plasma concentration of bupropion sustained-release (SR) is 85% that of immediate-release (IR). Bupropion HCl extended-release (ER) (Wellbutrin XL, generic) has been demonstrated to be equivalent to bupropion IR in terms of bioavailability and peak plasma concentrations. Studies have also shown bioequivalence of bupropion SR and bupropion ER. Bupropion HBr ER (Aplenzin) is an alcohol-resistant formulation. Bupropion HCl ER (Forfivo XL) has demonstrated bioequivalence to bupropion HCl ER (Wellbutrin XL, generic).

desvenlafaxine base and succinate (Desvenlafaxine ER, Pristiq)

Desvenlafaxine (O-desmethylvenlafaxine) is the major active metabolite of venlafaxine. Desvenlafaxine succinate (Pristiq, generic) and the base formulation (Desvenlafaxine ER) provide the same amount of desvenlafaxine. Desvenlafaxine base is not therapeutically equivalent to desvenlafaxine succinate (Pristiq, generic).

levomilnacipran (Fetzima)

Levomilnacipran is the more active of the 2 enantiomers present in milnacipran which is approved for the treatment of MDD outside the US; milnacipran is approved in the US only for the treatment of fibromyalgia. Levomilnacipran is not approved in the US for fibromyalgia. The absorption and bioavailability of levomilnacipran are not significantly affected by food. However, the extended-release formulation of levomilnacipran is affected by alcohol, which may result in a pronounced accelerated drug release, and the 2 should not be consumed concomitantly.

nefazodone

Food decreases the absorption and bioavailability of nefazodone by 20%. Liver cirrhosis increases its bioavailability by 25%. Nefazodone has a nonlinear pharmacokinetic profile due to autoinhibition via CYP3A.

selegiline (Emsam)

Selegiline transdermal (Emsam) results in significantly higher exposure to selegiline and lower exposure to its metabolites compared to oral dosing, where extensive first-pass metabolism occurs.

venlafaxine IR and venlafaxine ER (Effexor XR, Venlafaxine ER, generic)

Venlafaxine ER (Effexor XR, generic) has a slower rate of absorption and a lower peak plasma concentration than venlafaxine IR. The extent of absorption of the 2 dosage forms is equivalent.

vilazodone HCl (Viibryd)

Food (high fat or light meal) increases the absorption and bioavailability of vilazodone by 72%.

vortioxetine (Trintellix)

The absorption and bioavailability of vortioxetine are not affected by food.

CONTRAINDICATIONS/WARNINGS[125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148]

Boxed Warnings

Antidepressants have a boxed warning regarding the risk of suicide. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults compared to placebo in short-term studies of MDD and other psychiatric disorders. Anyone considering the use of any antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Selegiline transdermal system (Emsam) is contraindicated in patients < 12 years of age.

Tranylcypromine (Parnate) also carries a boxed warning informing that excessive consumption of foods or beverages that contain significant amounts of tyramine can precipitate hypertensive crisis. These foods should be avoided in patients treated with tranylcypromine while on therapy and for 2 weeks after discontinuation. For more information, see the Class Warnings section for MAOIs.

Esketamine (Spravato) carries a boxed warning for risk of dissociation and sedation after administration as well as abuse and misuse. Patients should be monitored for 2 hours following administration to mitigate these risks. Due to potential for abuse and misuse, practitioners should consider risks and benefits of prescribing and monitor for signs and symptoms of abuse and misuse.

Class Warnings

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed, although not established in controlled trials, that treating such an episode with an antidepressant alone may increase the likelihood of precipitating a mixed/manic episode in patients at risk for bipolar disorder. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history including a family history of suicide, bipolar disorder, and depression. The antidepressants in this review are not approved for use in treating bipolar depression.

The development of a potentially life-threatening serotonin syndrome may occur with MAOIs, SNRIs, SSRIs, and other serotonergic drugs like mirtazapine, vilazodone, or vortioxetine, particularly with concomitant use of other serotonergic drugs, including triptans, and with drugs which impair metabolism of serotonin, including MAOIs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Concomitant use of these agents with a triptan requires careful observation of the patient, particularly during treatment initiation and dosage increases. Concomitant use of these agents with serotonergic or anti-dopaminergic agents, including

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antipsychotics, should be discontinued immediately if signs of serotonin syndrome and/or neuroleptic malignant syndrome emerge. Serotonin syndrome may also occur when combined with amphetamines. These symptoms may include mental status changes, autonomic instability, neuromuscular aberrations, and/or gastrointestinal symptoms. Supportive symptomatic treatment should be initiated immediately.

SSRIs, SNRIs, and other antidepressants with serotonergic properties in this class may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages, including postpartum hemorrhage. Patients should be cautioned about the risk of bleeding associated with the concomitant use of any SSRI or SNRI and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

A gradual reduction in the dose of SNRIs rather than abrupt cessation is recommended whenever possible. A discontinuation syndrome has also been reported with non-SNRIs within this class.

Concomitant use of these agents with serotonin precursors (e.g., tryptophan) is not recommended.

Serotonergic drugs may cause hyponatremia resulting from development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The risk is highest in elderly patients, those requiring diuretic treatment, or in those with volume depletion.

Angle-closure glaucoma has been reported in patients with untreated anatomically narrow angles treated with antidepressants.

No agent in this class should be used in patients with known hypersensitivity to its active ingredient or excipient ingredients.

bupropion (Aplenzin, Forfivo XL, Wellbutrin SR, Wellbutrin XL, generic)

Bupropion HCl (Forfivo XL, Wellbutrin SR/XL, generic) and bupropion HBr (Aplenzin) are contraindicated in patients with a seizure disorder, anorexia and/or bulimia, or undergoing abrupt discontinuation of alcohol or sedatives. Bupropion is contraindicated in patients using other bupropion products, regardless of the indication (e.g., depression, smoking cessation). It is also contraindicated with MAOIs. Discontinuation of an MAOI for at least 2 weeks is required prior to initiating use of bupropion. Bupropion inhibits the reuptake of dopamine and norepinephrine and can increase the risk of hypertensive reactions when used with other drugs that also inhibit the reuptake of dopamine or norepinephrine (e.g., MAOIs including linezolid and intravenous methylene blue). Postmarketing reports in patients taking bupropion for smoking cessation include neuropsychiatric adverse events (e.g., changes in mood, psychosis, hallucinations, paranoia). These events have occurred in patients with and without preexisting conditions. Symptoms may resolve after discontinuing therapy, however, patients should be monitored as it is possible for symptoms to persist.

These agents are for oral use only; abuse by inhalation or injection of crushed, dissolved tablets has been reported and may result in seizures or even death.

desvenlafaxine base and succinate (Desvenlafaxine ER, Pristiq)

Desvenlafaxine is contraindicated for use in patients with hypersensitivity to desvenlafaxine, venlafaxine (venlafaxine IR, Effexor XR, Venlafaxine ER, generic), or any excipients in its formulation.

The concomitant use of desvenlafaxine with an MAOI is contraindicated. Do not use with an MAOI within 14 days of stopping an MAOI. Allow 7 days after stopping desvenlafaxine before starting an MAOI. Patients taking desvenlafaxine should not be started on linezolid or intravenous methylene blue. These drugs are MAOIs with indications other than psychiatric illness.

Mydriasis has been reported in association with desvenlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Desvenlafaxine should not be used concomitantly with other drugs containing desvenlafaxine or venlafaxine.

duloxetine (Cymbalta, Drizalma Sprinkle)

Duloxetine is contraindicated in patients with uncontrolled narrow-angle glaucoma.

Concomitant use of duloxetine with MAOIs, including linezolid and intravenous methylene blue, is contraindicated. At least 14 days should elapse between discontinuation of the MAOI and initiating duloxetine; at least 5 days should elapse between the discontinuation of duloxetine and initiating a MAOI. Twenty-four hours should elapse between the last dose of linezolid or intravenous methylene blue and resumption of therapy with duloxetine.

Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine, especially during the first week of therapy or after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension or are potent CYP1A2 inhibitors and in patients taking duloxetine at doses above 60 mg daily. Consider discontinuation of duloxetine in patients with symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

Duloxetine treatment relative to placebo has been associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. In clinical trials, there was no significant difference in the frequency of sustained elevated blood pressure (3 consecutive visits). Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.

Duloxetine should not be prescribed for patients with substantial alcohol use or evidence of chronic liver disease. Post-marketing reports indicated that elevated transaminases, bilirubin, and alkaline phosphatase have occurred when duloxetine has been given to such patients. There have been reports of hepatic failure, sometimes fatal, in patients treated with duloxetine.

Duloxetine has been known to affect urethral resistance. If symptoms of urinary hesitation develop with duloxetine, consideration should be given to the possibility that it might be drug-related.

In studies of diabetic peripheral neuropathic pain, duloxetine was associated with a small increase in mean fasting blood glucose as compared to placebo in a study of up to 52 weeks of therapy. The mean fasting blood glucose increased by 12 mg/dL in the duloxetine group and decreased by 11.5 mg/dL in the routine care group. HbA1c changes were +0.5% with duloxetine and +0.2% with the routine care group.

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Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome (SJS), have been reported with duloxetine. Duloxetine should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.

esketamine (Spravato)

In addition to use in patients with known hypersensitivity, esketamine is contraindicated in patients who have aneurysmal vascular disease or arteriovenous malformation or a history of intracerebral hemorrhage.

Esketamine causes an increase in blood pressure at all doses (8% to 19%), which peaks at approximately 40 minutes after administration and lasts approximately 4 hours. Patients with cardiovascular and cerebrovascular conditions should be carefully assessed prior to starting therapy and in patients whose blood pressure is elevated (> 140/90 mmHg), and a benefit versus risk analysis must be taken into account. Blood pressure should also be evaluated prior to every administration, and a decision to delay the dose may be warranted if blood pressure is elevated. Monitoring of blood pressure is required for 40 minutes following each dose and should be continued as clinically warranted. If blood pressure is decreasing and patient has been clinically stable for ≥ 2 hours, the patient can be discharged. Close monitoring is also necessary if esketamine is used concomitantly with stimulants or MAOIs.

More cases of short-term cognitive impairment were reported with esketamine in clinical trials 40 minutes post-dose compared to placebo; however, cognitive performance was comparable to placebo 2 hours post-administration. Long-term memory impairment has been reported with repeated ketamine misuse and/or abuse. Adverse effects from esketamine were not observed in a 1-year open-label safety study, but data beyond 1 year are unavailable.

Impaired ability to drive and/or operate machinery has been noted with esketamine; patients must be instructed not to engage in activities which require mental alertness and motor coordination until the next day, following a restful sleep. Likewise, transportation following treatment with esketamine must be arranged.

Cases of ulcerative or interstitial cystitis have been reported in patients using ketamine; however, no cases of esketamine-related interstitial cystitis were observed in any studies, which included treatment for up to 1 year. Due to a higher rate of lower urinary tract symptoms (e.g., pollakiuria, dysuria, micturition urgency, nocturia, cystitis) in esketamine-treated patients, ongoing monitoring for urinary tract and bladder symptoms during treatment may be clinically warranted.

Esketamine can cause fetal harm; pregnancy planning and prevention is advised.

levomilnacipran (Fetzima)

Levomilnacipran is contraindicated within 14 days of use of an MAOI. It is also contraindicated in a patients being treated with linezolid or intravenous methylene blue.

Similar to other SNRIs, levomilnacipran has been reported to cause an increase in blood pressure and heart rate. Blood pressure and heart rate should be monitored prior to and during therapy. Levomilnacipran should be used with caution in patients with pre-existing heart disease (hypertension, tachyarrhythmias, or cardiovascular disease). Patients with pre-existing seizure disorders were excluded from clinical trials and it should not be used in these patients. Levomilnacipran may increase urethral resistance; caution is advised in patients prone to obstructive urinary disorders.

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Because milnacipran has been reported to increase hepatic transaminases and cause fulminant hepatitis, levomilnacipran should be avoided in patients with a history of substantial alcohol use or chronic liver disease.

mirtazapine (Remeron, Remeron SolTab)

Mirtazapine is contraindicated for use within 14 days of initiating or discontinuing a MAOI.

Agranulosis and severe neutropenia were reported in pre-marketing clinical trials. If a patient develops a sore throat, fever, stomatitis, or other signs of infection and has a low white blood cell count, mirtazapine should be discontinued and the patient closely monitored.

Cases of QT interval (QT) prolongation, torsades de pointes, ventricular tachycardia, and sudden death have been reported with mirtazapine. Mirtazapine should be used cautiously in patients with a family history of QT prolongation or with known cardiovascular disease and in those taking concomitant QT-prolonging medications.

Other precautions include akathisia, somnolence, dizziness, increased appetite/weight gain, activation of mania, seizures, and laboratory abnormalities (e.g., transaminase elevations, elevated cholesterol, increased triglycerides).

nefazodone

Nefazodone has a boxed warning for life-threatening liver failure (risk of 1 case resulting in death or transplant per 250,000 to 300,000 years of nefazodone treatment).

MAOIs – isocarboxazid (Marplan), phenelzine (Nardil), selegiline (Emsam), tranylcypromine (Parnate)

MAOIs are contraindicated in patients with pheochromocytoma.

Isocarboxazid should not be used in patients who are hypersensitive to the drug or its ingredients, with a confirmed or suspected cerebrovascular defect, cardiovascular disease, hypertension, history of liver disease or abnormal liver function tests, or severely impaired renal function.

Phenelzine should not be used in patients who are hypersensitive to the drug or its ingredients or patients with congestive heart failure, severe renal impairment or renal disease, a history of liver disease, or abnormal liver function tests.

Tranylcypromine should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with cardiovascular disease, hypertension, or history of headache. Tranylcypromine should not be used in patients with a history of liver disease or in those patients with abnormal liver function tests.

Patients taking tranylcypromine or phenelzine should not undergo elective surgery requiring general anesthesia or receive cocaine or local anesthesia containing sympathomimetic vasoconstrictors. The possible combined hypotensive effects of MAOIs and spinal anesthesia should be kept in mind. MAOI therapy should be discontinued at least 10 days prior to elective surgery.

Phenelzine and tranylcypromine should not be administered in combination with MAOIs (including procarbazine [Matulane®]) or dibenzazepine derivatives. Dibenzazepine derivatives include the TCAs, carbamazepine, cyclobenzaprine, perphenazine, amoxapine, maprotiline, and mirtazapine. MAOIs should not be administered together or in rapid succession with other MAOIs or with dibenzazepine-

related entities. Hypertensive crises or severe convulsive seizures may occur in patients receiving such combinations. In patients being transferred to phenelzine or tranylcypromine from another MAOI or from a dibenzazepine-related entity, allow a medication-free interval of at least 7 days (tranylcypromine) to 10 days (phenelzine). MAOIs are contraindicated in patients receiving guanethidine.

MAOIs are contraindicated with bupropion products, buspirone, meperidine, and dextromethorphan. At least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with the contraindicated drugs.

MAOIs should not be administered in combination with any SSRI. There have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma in patients receiving fluoxetine in combination with a MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, fluoxetine and other SSRIs should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping fluoxetine before starting an MAOI.

At least 14 days should elapse between discontinuation of a MAOI and initiation of therapy with duloxetine, desvenlafaxine, trazodone, venlafaxine IR, venlafaxine ER (Effexor XR, Venlafaxine ER, generic), vortioxetine, levomilnacipran, or vilazodone. In addition, at least 5 days should be allowed after stopping duloxetine or venlafaxine/venlafaxine ER before starting an MAOI. At least 7 days should elapse between stopping desvenlafaxine or levomilnacipran and starting a MAOI, at least 14 days should elapse between discontinuation of vilazodone and starting a MAOI, and at least 21 days should elapse between discontinuation of vortioxetine and starting a MAOI. Concomitant use in patients taking MAOIs is contraindicated with duloxetine and venlafaxine products due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs.

MAOIs should not be administered in combination with sympathomimetics, including amphetamines, cocaine, methylphenidate, dopamine, epinephrine, norepinephrine or related compounds, and cold, hay fever, or weight-reducing preparations that contain vasoconstrictors.

The most important reaction associated with MAOIs administration is the occurrence of hypertensive crises, which have sometimes been fatal. These crises are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain. Blood pressure should be monitored. Therapy should be discontinued immediately upon the occurrence of palpitation or frequent headaches during therapy.

Hypertensive crises have sometimes occurred during therapy with MAOIs after ingestion of foods with high tyramine content. In general, the patient should avoid protein foods in which aging or protein breakdown is used to increase flavor such as cheese, sour cream, certain wines, sherry, beer, liqueurs, pickled herring, anchovies, caviar, liver, canned figs, dried fruits, bananas, raspberries, avocados, overripe fruit, chocolate, soy sauce, sauerkraut, dry sausage, the pods of broad beans, yeast extracts, yogurt, meat extracts, or meat prepared with tenderizers. Excessive amounts of caffeine should be avoided. Data for selegiline (Emsam) transdermal 6 mg/24 hours support the recommendation that a

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modified diet is not required at this dose. Patients receiving higher doses should follow the standard dietary modifications for patients taking MAOIs.

trazodone

The QT/corrected QT (QTc) interval can be prolonged by use of trazodone. This may lead to torsades de pointes or arrhythmias. Orthostatic hypotension and syncope have also been reported with trazodone use.

venlafaxine IR and venlafaxine ER (Effexor XR, Venlafaxine ER, generic)

Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Venlafaxine therapy is associated with sustained hypertension which is defined as supine diastolic blood pressure ≥ 90 mm Hg and ≥ 10 mm Hg above baseline on 3 consecutive visits. Venlafaxine IR studies revealed a dose-dependent increase in blood pressure (placebo: 2%; venlafaxine IR doses < 100 mg daily: 3%; > 100 to ≤ 200 mg daily: 5%; > 200 to ≤ 300 mg daily: 7%; and doses exceeding 300 mg daily: 13%). In pre-marketing studies with venlafaxine ER (Effexor XR) in MDD, 0.7% of patients discontinued treatment because of elevated blood pressure. Pre-existing hypertension should be controlled before treatment with venlafaxine. Blood pressure should be monitored on a regular basis.

vilazodone HCl (Viibryd)

Serotonin syndrome or neuroleptic malignant syndrome can occur with vilazodone; if this occurs, the drug should be discontinued and supportive treatment administered. Vilazodone should not be used in patients being treated with MAOIs including those not being used to treat psychiatric conditions, such as linezolid or methylene blue. Vilazodone should be used with caution in patients with seizure disorders due to its ability to cause seizures. Vilazodone can cause activation of mania or hypomania, and patients should be screened for bipolar disorder. Vilazodone can increase the risk of bleeding and should be used with caution in patients receiving other drugs that affect coagulation. Post-marketing reports of bruxism have been reported.

vortioxetine (Trintellix)

Vortioxetine is contraindicated within 21 days of an MAOI or in a patient being treated with linezolid or intravenous methylene blue.

The warnings and precautions for use of vortioxetine are consistent with the class warnings observed with other serotonergic drugs (described above).

Risk Evaluation and Mitigation Strategies (REMS)[149]

Use of esketamine (Spravato) requires enrollment in the Spravato REMS program in order to mitigate the serious adverse reactions that can result from the sedation and dissociation associated with esketamine use. The REMS program requires enrollment and education of the patient, healthcare setting for administration (including staff training, an authorized representative, patient monitoring and patient enrollment verification), and dispensing pharmacy in order to support the safe use of esketamine.

DRUG INTERACTIONS[150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167, 168,169,170,171,172,173]

The non-MAOI drugs in this class should not be used concomitantly or within 2 weeks of stopping an MAOI. Additionally, when converting from an MAOI to 1 of these antidepressants, there must be a washout period of 7 to 21 days, depending on the specific drug. This interaction warning also applies to other non-psychiatric medications with MAOI properties, such as linezolid and intravenous methylene blue.

A more extensive discussion is located in the *Contraindications/Warnings* section above.

The development of a potentially life-threatening serotonin syndrome may occur with SNRIs, SSRIs, or other serotonergic antidepressant treatment, particularly with concomitant use of serotonergic drugs in other classes, including triptans, and select other drug classes (e.g., amphetamines).

Serotonergic drugs may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk.

These products have inhibition potential at CYP450 enzyme systems at usual doses.[174,175]

Drug	1A2	2C9/19	2B6	2D6	3A4
bupropion HBr (Aplenzin)	--	--	low	low	--
bupropion HCl (generic, Wellbutrin SR/XL, Forfivo XL)	--	Low	low	low	low
desvenlafaxine base (desvenlafaxine ER) desvenlafaxine succinate (Pristiq)	--	--	--	low	low
duloxetine (Cymbalta, Drizalma Sprinkle)	--	--	--	moderate	--
esketamine (Spravato)	--	--	--	--	--
isocarboxazid (Marplan)	--	--	--	--	--
levomilnacipran (Fetzima)	--	--	--	--	--
mirtazapine (Remeron, Remeron SolTab)	low	low	--	low	low
nefazodone	low	low	--	low	high
phenelzine (Nardil)	--	--	--	--	--
selegiline (Emsam)	--	--	--	--	--
tranylcypromine (Parnate)	--	--	--	--	--
trazodone	--	--	--	--	low
venlafaxine (venlafaxine IR, Effexor XR, Venlafaxine ER)	--	--	--	low	--
vilazodone HCl (Viibryd)	--	--	--	--	--
vortioxetine (Trintellix)	--	--	--	--	--

-- = no or negligible inhibition; Low = 20-50% inhibition; Moderate = 50-100% inhibition; High = 100-150% inhibition

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bupropion (Aplenzin, Forfivo XL, Wellbutrin SR, Wellbutrin XL, generic)

- Drugs metabolized by CYP2D6 – use concurrently with caution; use lower dose of concomitant medication
- Levodopa, amantadine – higher incidence of adverse effects
- Drugs that lower seizure threshold – increases the incidence of bupropion-related seizures
- Other dopamine agonists and norepinephrine antagonists – potentiation and reduction in the effects of these drugs may occur when administered with bupropion
- Ritonavir, ritonavir plus lopinavir, and efavirenz reduced the exposure of bupropion and its major metabolites in a dose-dependent manner; this is possibly due to the induction of bupropion metabolism
- Desvenlafaxine base and succinate (Desvenlafaxine ER, Pristiq, generic) – Drugs metabolized by CYP2D6 – concomitant use of drugs metabolized by CYP2D6 may result in higher concentrations of that drug
- Drugs metabolized by CYP3A4 – concomitant use of drugs metabolized by CYP3A4 may result in lower concentrations of that drug and alternatively higher concentrations of desvenlafaxine
- Data from literature suggest that concomitant use of bupropion and digoxin may decrease digoxin plasma levels

duloxetine (Cymbalta, Drizalma Sprinkle)

- Inhibitors of CYP2D6 – concomitant use increases duloxetine concentration
- Inhibitors of CYP1A2 – concomitant use increases duloxetine concentration
- Drugs metabolized by CYP2D6 – duloxetine is a moderate inhibitor of CYP2D6 and increases the area under the curve (AUC) and maximum serum concentration (Cmax) of drugs metabolized by this enzyme; use with caution
- Drugs that raise the gastric pH – duloxetine is enteric-coated and drugs that raise gastric pH may lead to early release of duloxetine
- Drugs that are highly protein-bound – duloxetine is highly protein-bound and administration with another highly protein-bound drug may increase free concentrations of the other drug

esketamine (Spravato)

- Concomitant CNS depressants – closely monitor for increased sedation
- Concomitant psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) – may increase blood pressure; monitor closely
- Nasal corticosteroids or nasal decongestants – administer ≥ 1 hour prior to administration of esketamine

isocarboxazid (Marplan)

- Disulfiram (Antabuse®) co-administration – cautious administration and monitoring suggested
- Combination therapy with other psychotropics – generally not recommended and 10-day wash-out interval suggested to avoid concomitant use

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levomilnacipran (Fetzima)

- Strong inhibitors of CYP3A4 – levomilnacipran's metabolism may be decreased by strong inhibitors of CYP3A4 (ketoconazole) resulting in a clinically meaningful increase in levomilnacipran exposure
- Alcohol affects the extended-release properties of levomilnacipran and levomilnacipran should not be taken with alcohol

mirtazapine (Remeron, Remeron Soltab)

- Strong inhibitors of CYP3A4 – may increase mirtazapine exposure; decrease dose if needed
- Cimetidine (inhibitor of CYP1A2, CYP2D6, and CYP3A) – may increase mirtazapine exposure; decrease dose if needed
- CNS depressants – increased risk of cognitive and motor skill impairment; avoid use
- QT prolonging agents – additive risk of QT prolongation; use cautiously
- Warfarin – concomitant use may increase international normalized ratio (INR); monitor INR

nefazodone

- Drugs that are metabolized by CYP3A4 – nefazodone inhibits the metabolism and increases the bioavailability of drugs metabolized by that enzyme; caution must be used when using nefazodone concurrently with these drugs
- Carbamazepine – the bioavailability of nefazodone is reduced by 95% when used concurrently with carbamazepine

selegiline (Emsam)

- Contraindications – SSRIs, SNRIs, mirtazapine, TCAs, bupropion, meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John's wort, cyclobenzaprine, carbamazepine, oxcarbazepine, sympathomimetic amines, general anesthesia

trazodone

- CYP3A4 inhibitors – can inhibit the metabolism of trazodone
- CYP3A4 inducers – can induce the metabolism of trazodone
- Phenytoin – elevated levels of phenytoin have been reported with concurrent use
- CNS depressants – trazodone may enhance the response to these products

venlafaxine (venlafaxine IR, Effexor XR, Venlafaxine ER, generic)

- Haloperidol – the clearance of haloperidol is reduced and bioavailability increased
- Ketoconazole – increased concentrations of venlafaxine and O-desmethyl venlafaxine
- Due to lack of test specificity, false-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. False-positive test results may result even following discontinuation of bupropion therapy. Similarly, false-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported with venlafaxine and desvenlafaxine which persist for several days following discontinuation of the drug.

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Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion, venlafaxine, or desvenlafaxine from amphetamines or PCP.

vilazodone HCl (Viibryd)

- CYP3A4 moderate to strong inhibitors – co-administration with strong inhibitors (e.g., ketoconazole) can increase vilazodone plasma concentrations by approximately 50%; vilazodone dose reduction is recommended. Moderate inhibitors of CYP3A4 (e.g., erythromycin) may increase vilazodone concentrations; vilazodone dose reduction is recommended if intolerable adverse reactions occur. No dose reduction is indicated when co-administered with mild inhibitors.

- CYP3A4 inducers – the effect of CYP3A4 induction on vilazodone concentrations has not been studied

- Drugs that interfere with hemostasis – platelet release of serotonin plays an important role in hemostasis. Drugs that interfere with serotonin reuptake have been associated with gastrointestinal bleeding, and concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin may potentiate the bleeding risk. SSRIs and SNRIs have been shown to increase bleeding risk when co-administered with warfarin, and warfarin therapy should be closely monitored if vilazodone is used with warfarin.

- Serotonergic drugs – vilazodone has the potential to cause serotonin syndrome if co-administered with other drugs that affect the serotonergic neurotransmitter system

- Drugs that are highly protein-bound – vilazodone is highly protein-bound, and administration with another highly protein-bound drug may increase free concentrations of the other drug

vortioxetine (Trintellix)

- A dosage reduction of 50% should be considered if vortioxetine is administered with a strong CYP2D6 inhibitor, such as bupropion, fluoxetine, paroxetine, or quinidine

- Strong inducers of CYP – consider increasing the dose of vortioxetine when a strong inducer of cytochrome P450 enzymes (e.g., rifampin, carbamazepine, phenytoin) is administered concurrently for longer than 14 days

- Co-administration of vortioxetine with other highly protein-bound drugs may result in an increase in the other drug's free concentration

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ADVERSE EFFECTS[176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199]

Drug	Weight Loss	Weight Gain	Dry Mouth	Nausea	Headache	Agitation	Insomnia	Somnolence	Withdrawals Due to AE
bupropion HBr ER (Aplenzin)*	nr	nr	≥ 5	≥ 5	nr	≥ 5	≥ 5	nr	nr
bupropion HCl IR	23-28 (14-23)	9-14 (23)	28 (10-18)	23 (19)	26 (22)	32 (22)	19-29 (16)	nr	10 (<10)
bupropion HCl SR (Wellbutrin SR)	14-19 (6)	2-3 (4)	17-24 (7)	13-18 (8)	25-26 (23)	3-9 (2)	11-16 (6)	2-3 (2)	0-2.4 (0.3)
bupropion HCl XL (Wellbutrin XL, Forfivo XL) **	23 (11)	11 (21)	26 (15)	13 (8)	34 (26)	2 (<1)	20 (13)	nr	9 (5)
desvenlafaxine ER base	0.4-1.1 (0)	nr	11-25 (9)	22-41 (10)	2	nr	9-15 (6)	4-12 (4)	4.1-12 (3-3.8)
desvenlafaxine succinate ER (Pristiq)	1-2 (1)	reported	11-25 (9)	22-41 (10)	20-29 (23)	reported	9-15 (6)	4-12 (4)	4.1-12 (3-3.8)
duloxetine (Cymbalta, Drizalma Sprinkle)	reported	nr	14 (6)	25 (9)	16 (15)	reported	11 (7)	11 (3))	9-19.5 (4-11.8)
esketamine (Spravato)	nr	nr	4-5 (3)	27-32 (9-14)	20 (17)	13-15 (6-9) (reported as anxiety)	8 (7)	23-29 (9-12)	2.6-4.6 (1.4-2.1)
isocarboxazid (Marplan)	nr	nr	6-9 (4)	4-6 (2)	6-15 (13)	nr	4-6 (4)	0-4 (0)	2-12 (5)
levomilnacipran (Fetzima)	nr	nr	nr	17 (6)	nr	nr	nr	nr	9 (3)
mirtazapine (Remeron, Remeron SolTab)	nr	12 (2)	25 (15)	reported	reported	reported	nr	54 (18)	1.5-16 (0-7)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

*The most common adverse reactions associated with Aplenzin are twice the placebo rate or more.

**Forfivo XL is bioequivalent to Wellbutrin XL.

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Adverse Effects (continued)

Drug	Weight Loss	Weight Gain	Dry Mouth	Nausea	Headache	Agitation	Insomnia	Somnolence	Withdrawals Due to AE
nefazodone	nr	nr	25 (13)	22 (12)	36 (33)	nr	11 (9)	25 (14)	16 (nr)
phenelzine (Nardil)	nr	reported	reported	nr	reported	nr	reported	nr	nr
selegiline (Emsam)	nr	nr	8 (6)	nr	18 (17)	nr	12 (7)	nr	7.1 (3.6)
tranylcypromine (Parnate)	nr	nr	reported	reported	reported	reported	reported	nr	nr
trazodone	6 (3)	5 (2)	34 (20)	13 (10)	20 (16)	nr	6 (12)	up to 40	nr
venlafaxine IR	1	reported	22 (11)	37 (11)	25 (24)	2	18 (10)	23 (9)	19
venlafaxine ER (Effexor XR, Venlafaxine ER)	3	> 1	12 (6)	31 (12)	> 2	3 (1)	17 (11)	17 (8)	7-18 5-12
vilazodone HCl (Viibryd)	nr	nr	8 (5)	23 (5)	nr	nr	6 (2)	3 (2)	7.1 (3.2)
vortioxetine (Trintellix)	nr	nr	6-8 (6)	21-32 (9)	nr	nr	nr	nr	5-8 (4)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

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bupropion (Aplenzin, Forfivo XL, Wellbutrin SR/XL, generic)

There is a dose-related risk of seizures with the use of bupropion. Seizures occur in roughly 0.1% of patients receiving bupropion SR up to 300 mg/day and 0.5% of patients receiving bupropion IR up to 450 mg/day. The incidence of seizures increases disproportionately at bupropion IR dosages above 450 mg/day.[200] In patients receiving bupropion IR 600 mg/day, the risk of seizures was estimated to be 10 times that of patients receiving the maximum daily recommended dose of 450 mg. According to the manufacturer, the incidence of seizures in patients taking bupropion ER as a single-dose of 450 mg is 0.4%.

When used for smoking cessation, postmarketing reports have shown bupropion to have an increased risk in neuropsychiatric events in patients with or without preexisting psychiatric disease. Reported cases range from mood changes, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, suicidal ideation, suicide attempt, and completed suicide. Patients should be monitored until resolution of symptoms, which usually occurs after discontinuation.

desvenlafaxine base and succinate (Desvenlafaxine ER, Pristiq)

Cautious use in patients with bipolar disorder, cardiovascular/cerebrovascular disease, and lipid metabolism disorders is recommended.

Dose-related elevations in fasting serum total cholesterol, low density lipoprotein cholesterol (LDL-C), and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with desvenlafaxine.

Postmarketing reports of acute pancreatitis, Steven-Johnson syndrome, and Takotsubo cardiomyopathy have occurred.

duloxetine (Cymbalta, Drizalma Sprinkle)

Duloxetine increases the risk of elevation of serum transaminase levels. In clinical trials, 1% of patients treated with duloxetine had an elevation of alanine aminotransferase (ALT) over 3 times the upper limit of normal compared to 0.2% of patients receiving placebo. Duloxetine is not recommended for use in patients with hepatic insufficiency or who use substantial amounts of alcohol.

Postmarketing reports of acute pancreatitis, gastrointestinal hemorrhage, myocardial infarction and Takotsubo cardiomyopathy have occurred.

esketamine (Spravato)

The most common (incidence > 10% in at least 1 of the major trials for approval) adverse effects reported with esketamine in clinical trials and not reported above were dissociation, dizziness, vertigo, dysgeusia, hypoesthesia, lethargy, vomiting, and increased blood pressure.

isocarboxazid (Marplan)

Isolated cases of akathisia, ataxia, black tongue, coma, dysuria, euphoria, hematologic changes, incontinence, neuritis, photosensitivity, sexual disturbances, spider telangiectasias, and urinary retention have been reported. These adverse effects may necessitate discontinuation of therapy. In rare instances, hallucinations have been reported with high doses, but they have disappeared upon dose reduction or discontinuation of therapy.

levomilnacipran (Fetzima)

The most common adverse events reported in clinical trials of levomilnacipran (incidence ≥ 5% and at least twice the rate of placebo) were nausea, constipation, hyperhidrosis, heart rate increase, erectile dysfunction, tachycardia, vomiting, and palpitations. Erectile dysfunction and urinary retention appear to be dose related.

Postmarketing reports of Takotsubo cardiomyopathy have occurred in patients taking milnacipran. Due to pharmacological similarities between the 2 agents, the potential for occurrence may be extrapolated to levomilnacipran.

mirtazapine (Remeron, Remeron SolTab)

In pre-marketing trials, 2 out of 2,796 patients developed agranulocytosis, and a third patient developed severe neutropenia. All 3 patients recovered upon discontinuation of mirtazapine. These cases yield a crude incidence of severe neutropenia of approximately 1.1 per 1,000 patients (95% CI, 0.2 to 3.1 cases per 1,000). In clinical trials, nonfasting cholesterol elevations to 20% of the upper limit of normal were observed for 15% of patients treated with mirtazapine compared to 7% of patients treated with placebo. Nonfasting triglyceride elevations to 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% of patient receiving placebo. ALT elevations to 3 times the upper limit of normal were observed in 2% of patients exposed to mirtazapine compared to 0.3% of placebo patients. Postmarketing cases of ventricular arrhythmia, severe skin reactions, increased creatine kinase and rhabdomyolysis, hyperprolactinemia, priapism, and somnambulism have been reported with mirtazapine.

nefazodone

There have been reports of adverse liver toxicities with nefazodone. Nefazodone has been removed from the European market based on deaths due to liver failure. Petitions have also been sent to the FDA asking for removal of this product from the US market.

selegiline (Emsam)

Application site reactions have been reported in 24% to 36% of patients receiving selegiline transdermal patches, compared to 12 to 17% of patients receiving placebo patches; rash occurred in 4% and 2% of patients, respectively.[201,202]

trazodone

Trazodone is associated with the occurrence of sexual dysfunction, including priapism, ejaculation disorders, erectile dysfunction, and decreased libido.

venlafaxine ER (Effexor XR, Venlafaxine ER, generic)

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and none of the placebo-treated patients for at least 3 months.

There have been spontaneous reports of adverse events occurring upon discontinuation (particularly when abrupt) of the SNRIs. Adverse events include dysphoria, irritability, agitation, dizziness, sensory disturbances, confusion, headache, lethargy, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms

reported. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

Postmarketing reports of Takotsubo cardiomyopathy have occurred.

vilazodone HCl (Viibryd)

In clinical trials, the most common adverse reactions occurring in greater than 5% of patients and in at least twice the rate as in the placebo group were diarrhea (28%), nausea (23%), vomiting (5%), and insomnia (6%). These adverse reactions are similar in nature to those reported with the SSRIs and SNRIs.

Discontinuation symptoms have been reported when other serotonergic drugs are abruptly stopped so gradual reduction is recommended, whenever possible.

Postmarketing adverse effects include pancreatitis and sleep paralysis.

vortioxetine (Trintellix)

In short-term (6- to 8-week) clinical trials, the most common adverse reactions with an incidence of greater than or equal to 5% and at least twice the rate of placebo were nausea, constipation, and vomiting. Nausea was dose-related and typically experienced during treatment initiation (median duration 2 weeks). Approximately 10% of patients reported nausea at the end of the 6 to 8 week trial.

Discontinuation symptoms have been reported following abrupt discontinuation of 15 to 20 mg/day dosages.

Sexual dysfunction may occur with vortioxetine; however, rates have been found to be lower compared to select SSRIs.

No significant effect on body weight was reported in clinical trials of vortioxetine; however, weight gain has been reported since its approval.

Postmarketing reports of acute pancreatitis, seizures, and rash have occurred.

Suicidality

A meta-analysis of randomized controlled trials (RCTs) assessed the efficacy and risk of reported suicidal ideation/suicide attempt of antidepressants for treatment of pediatric MDD, obsessive-compulsive disorder (OCD), and non-OCD anxiety disorders.[203] Studies were published and unpublished randomized, placebo-controlled, parallel-group trials of second generation antidepressants (SSRIs, nefazodone, venlafaxine, and mirtazapine) in participants younger than 19 years of age. Selection included 27 trials of pediatric MDD (n=15), OCD (n=6), and non-OCD anxiety disorders (n=6), and risk differences for response and for suicidal ideation/suicide attempt were estimated by random-effects methods. Pooled risk differences in rates of primary study-defined measures of responder status significantly favored antidepressants for MDD (11%; 95% CI, 7.1 to 14.9), OCD (19.8%; 95% CI, 13 to 26.6), and non-OCD anxiety disorders (37.1%; 95% CI, 22.5 to 51.7), corresponding to a number needed to treat of 10 (95% CI, 7 to 15), 6 (95% CI, 4 to 8) and 3 (95% CI, 2 to 5), respectively. While there was increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug versus placebo, the pooled risk differences within each indication were not statistically significant. There were no completed suicides. Age-stratified analyses showed that for children younger than 12 years of age with MDD, only fluoxetine showed benefit over placebo. In MDD trials, efficacy was

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moderated by age, duration of depression, and number of sites in the treatment trial. Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. Benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.

SPECIAL POPULATIONS[204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221, 222,223,224,225,226,227]

Pediatrics

All of the antidepressants in this class have a boxed warning regarding suicidality in children, adolescents, and young adults.

Safety and effectiveness in the pediatric population have not been established for nearly all products in this class, excluding selegiline and duloxetine. Transdermal selegiline (Emsam) use is contraindicated at any dose in children under the age of 12, even with dietary modification. Pharmacokinetic data in children < 12 years of age suggests that even the lowest dose of commercially available Emsam may result in higher levels of selegiline than those seen in adolescents or adults. Thus, these children may be at an increased risk of hypertensive crisis. Duloxetine (Cymbalta, Drizalma Sprinkle) is approved for use for generalized anxiety disorder in pediatric patients ≥ 7 years of age, and duloxetine (Cymbalta) is approved for fibromyalgia in pediatric patients ≥ 13 years of age.

Although no studies have been designed to primarily assess venlafaxine's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that venlafaxine may adversely affect weight and height.

Pregnancy

For ethical reasons, double-blind, randomized studies of antidepressant drug effects on the fetus and mother are unavailable. Based on animal data, the FDA classified all of the drugs in this class in originally as Pregnancy Category C. Safety of phenelzine (Nardil) and tranylcypromine (Parnate) for use by pregnant women has not been established. Isocarboxazid (Marplan) should be given to a pregnant woman only if clearly needed. As drug labeling is updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR), assigned Pregnancy Categories have been replaced with descriptive text. This has occurred with bupropion (generic, Aplenzin, Forfivo XL, Wellbutrin SR, Wellbutrin XL), desvenlafaxine (Desvenlafaxine ER), desvenlafaxine succinate (Pristiq), duloxetine (Cymbalta), isocarboxazid (Marplan), levomilnacipran (Fetzima), mirtazapine (Remeron, Remeron SolTab), phenelzine (Nardil), selegiline (Emsam), tranylcypromine (Parnate), trazodone, vilazodone (Viibryd), and vortioxetine (Trintellix). Data are too limited on use during pregnancy to inform of any drug-associated risks with these products. Limited data with bupropion in the first trimester have not found of congenital malformations. Limited data from published studies have not identified a clear drug-associated risk to the mother or fetus in pregnant women taking duloxetine. Neither esketamine (Spravato) nor duloxetine delayed-release (Drizalma Sprinkle) were assigned a Pregnancy Category upon approval in compliance with the PLLR. As esketamine can cause fetal harm based on limited animal data, pregnancy planning and prevention is advised during esketamine use. Nefazodone and venlafaxine (venlafaxine, Venlafaxine ER, Effexor XR) remain Pregnancy Category C agents.

Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with SNRIs or SSRIs, the physician should carefully consider the potential risks and benefits of treatment. Consider tapering therapy during the third trimester. Postpartum hemorrhage has also been reported with agents within this class. The risk of untreated depression must also be considered. Healthcare providers are encouraged to register patients with the National Pregnancy Registry for Antidepressants.

Renal Impairment

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. It should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered. Bupropion ER (Forfivo XL) is only available as a single strength 450 mg dose and is not recommended for use in patients with renal impairment.

Desvenlafaxine (Desvenlafaxine ER, Pristiq) requires a dose adjustment (maximum of 50 mg/day) in patients with moderate renal impairment (creatinine clearance [CrCl], 30 to 50 mL/min) and a dose adjustment (maximum of 25 mg/day or 50 mg every other day) in patients with severe renal impairment (CrCl, 15 to 29 mL/min) or end-stage renal disease (ESRD; CrCl, < 15 mL/min). Supplemental doses after dialysis are not needed.

Duloxetine (Cymbalta, Drizalma Sprinkle) is not recommended for patients with ESRD or severe renal impairment (estimated creatinine clearance < 30 mL/min).

Isocarboxazid should not be used in patients with severe renal impairment.

In patients with moderate renal impairment (CrCl, 30 to 59 mL/min), the levomilnacipran dose should be not exceed 80 mg/day and for those with severe renal impairment (CrCl, 15 to 30 mL/min), the maximum daily dose should be 40 mg/day.

Caution is indicated in administering mirtazapine (Remeron, Remeron SolTab, generic) to patients with compromised renal function since its elimination is correlated with creatinine clearance.

Hepatic Impairment

In patients with moderate to severe hepatic impairment, a reduced dose and/or frequency of bupropion is required. Bupropion should be used with caution in patients with mild impairment, and a reduced frequency and/or dose should be considered. All patients with hepatic impairment should be closely monitored for possible adverse effects. Bupropion ER (Forfivo XL) is only available in 450 mg tablet, since there is no lower dose strength it is not recommended for use in patients with hepatic impairment.

Desvenlafaxine does not require a dosage adjustment in starting dosage for patients with hepatic disease. The maximum dosage for patients with moderate to severe hepatic impairment (Child-Pugh score of 7 to 15) is 50 mg daily.

Duloxetine should not be administered to patients with hepatic insufficiency as it increases the risk of elevation of serum transaminase levels. Duloxetine should also not ordinarily be administered to patients with substantial alcohol use.

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No dose adjustments of esketamine (Spravato) are necessary for patients with mild to moderate hepatic impairment, although patients with moderate impairment (Child-Pugh B) may need additional monitoring for adverse reactions. Esketamine has not been studied in patients with severe hepatic impairment (Child-Pugh C); use in this population is not recommended.

Isocarboxazid should not be used in patients with a history of liver disease or in those with abnormal liver function tests.

Hepatic elimination plays a minimal role in the elimination of levomilnacipran; no dose adjustment is recommended in patients with mild to severe impairment.

Caution is indicated in administering mirtazapine to patients with compromised hepatic function.

Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The physician may consider the value of liver function testing for patients treated with nefazodone, and patients should be advised to be alert for signs and symptoms of liver dysfunction such as jaundice, anorexia, gastrointestinal complaints, and malaise and to report them to their doctor immediately should they occur. Nefazodone should be withdrawn if evidence of hepatocellular injury, such as increased serum aspartate transaminase (AST) or ALT levels greater than 3 times the upper limit of normal develop, and these patients should be presumed to be at increased risk for liver injury if the drug is reinitiated; therefore, these patients should not be considered for re-treatment.

Dosage adjustment for venlafaxine is necessary in hepatically impaired patients as it is well absorbed and extensively metabolized by the liver.

The dosage of vilazodone (Viibryd) does not need adjustment in patients with mild-to-moderate hepatic dysfunction. Whether the dosage needs to be adjusted in patients with severe hepatic dysfunction is unknown.

The dosage of vortioxetine does not need adjustment in patients with renal dysfunction or mild-to-severe hepatic dysfunction.

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DOSAGES[228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251]

Drug	Starting Dose	Maintenance Dose	Maximum Dose	Hepatic Impairment	Renal Impairment	Dosage Forms
bupropion HBr ER (Aplenzin)	174 mg every morning (equivalent to 150 mg bupropion HCl)	Periodic assessment for maintenance dose determination	522 mg once daily (equivalent to 450 mg bupropion HCl)	↓	↓	ER tablets: 174 mg, 348 mg, 522 mg
bupropion HCl ER (Forfivo XL)	450 mg once daily	450 mg once daily	450 mg once daily	drug not recommended	drug not recommended	ER Tablet: 450 mg
bupropion HCl ER (Wellbutrin XL)	150 mg every morning	300 mg every morning	450 mg every morning	↓	↓	ER tablets: 150 mg, 300 mg
bupropion HCl IR	100 mg twice daily	100 mg 3 times daily	150 mg 3 times daily	↓	↓	Tablets: 75 mg, 100 mg
bupropion HCl SR (Wellbutrin SR)	150 mg every morning	150 mg twice daily	200 mg twice daily	↓	↓	SR tablets: 100 mg, 150 mg, 200 mg
desvenlafaxine ER base (Desvenlafaxine ER)	50 mg daily	50 mg to 400 mg daily	400 mg daily	↓	↓	ER tablets as free base: 50 mg, 100 mg
desvenlafaxine succinate ER (Pristiq)	50 mg daily	50 mg to 400 mg daily	400 mg daily	↓	↓	ER tablets as succinate: 25 mg, 50 mg, 100 mg
duloxetine (Cymbalta)	MDD: 20 to 30 mg twice daily All other diagnoses: 60 mg/day May start at 30 mg once daily for 1 week	60 mg/day in 1 or 2 doses	MDD and GAD: 120 mg/day All other diagnoses: 60 mg/day	drug not recommended	↓ drug not recommended with severe impairment	Capsules: 20 mg, 30 mg, 40 mg[*] (generic only), 60 mg
duloxetine delayed-release (Drizalma Sprinkle)	MDD: 20 mg twice daily or 60 mg/day in 1 or 2 doses GAD: 60 mg once daily May start at 30 mg once daily for 1 week	MDD: 40 mg/day to 60 mg/day in 1 or 2 doses GAD: 60 mg/day	MDD and GAD: 120 mg/day All other diagnoses: 60 mg/day	drug not recommended	↓ drug not recommended with severe impairment	Delayed-release capsules: 20 mg, 30 mg, 40 mg, 60 mg

Doses are FDA-approved doses for outpatients.

-- = no dosage change required; ↓ = consideration should be given to reducing the dose and/or dosage frequency; nr = not reported

*Irenka™ (duloxetine) by Lupin was approved via an abbreviated new drug application (ANDA) using Cymbalta (duloxetine) as the reference drug; it was marketed under the trade name Irenka and was uniquely available as a 40 mg capsule. Irenka has since been discontinued, but other generic 40 mg formulations, including one by Lupin, are available.

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Drug	Starting Dose	Maintenance Dose	Maximum Dose	Hepatic Impairment	Renal Impairment	Dosage Forms
esketamine (Spravato)	TRD – Induction Phase: Day 1: 56 mg Weeks 1 through 4: 56 mg or 84 mg twice weekly Acute suicidal thoughts or behaviors: 84 mg twice weekly for 4 weeks	TRD – Maintenance Phase: Weeks 5 through 8: 56 mg or 84 mg once weekly Weeks ≥ 9: 56 mg or 84 mg every 1 to 2 weeks Acute suicidal thoughts or behaviors: reevaluate treatment; use has not been evaluated for > 4 weeks	84 mg twice weekly	not recommended in Child-Pugh C	--	Nasal spray: 28 mg/ device; each device delivers 2 sprays (14 mg/spray); Available in kits of 2 (56 mg) or 3 (84 mg) nasal devices
isocarboxazid (Marplan)	10 mg twice daily	Periodic assessment with incremental dose increases up to 20 mg/week	60 mg/day in 2 to 4 doses	drug not recommended	drug not recommended	Tablets: 10 mg
levomilnacipran (Fetzima)	20 mg daily for 2 days, then 40 mg daily	40 mg to 120 mg once daily, increase in increments of 40 mg at intervals of ≥ 2 days	120 mg once daily	--	↓	ER capsules: 20 mg, 40 mg, 80 mg, 120 mg Titration Pack: two 20 mg and twenty-six 40 mg capsules
mirtazapine (Remeron, Remeron SolTab)	15 mg every evening	15 mg to 45 mg every evening	45 mg every evening	↓	↓	Tablets: 7.5 mg (generic only), 15 mg, 30 mg, 45 mg (generic only) Orally dissolving tablets: 15 mg, 30 mg, 45 mg

Doses are FDA-approved doses for outpatients.

-- = no dosage change required; ↓ = consideration should be given to reducing the dose and/or dosage frequency;

nr = not reported

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Dosages (continued)

Drug	Starting Dose	Maintenance Dose	Maximum Dose	Hepatic Impairment	Renal Impairment	Dosage Forms
nefazodone	100 mg twice daily	150 mg to 300 mg twice daily	300 mg twice daily	↓	↓	Tablets: 50 mg, 100 mg, 150 mg, 200 mg, 250 mg
phenelzine (Nardil)	15 mg 3 times daily	15 mg to 60 mg per day	90 mg per day in divided doses	nr	nr	Tablets: 15 mg
selegiline (Emsam)	6 mg patch daily	6 mg patch daily	12 mg patch daily	--	--	Patches: 6 mg/24 hours, 9 mg/24 hours, 12 mg/24 hours
tranylcypromine (Parnate)	30 mg daily in divided doses	30 mg daily in divided doses	60 mg daily in divided doses	nr	nr	Tablets: 10 mg
trazodone	150 mg/day in divided doses	150 to 400 mg/day in divided doses	400 mg/day in divided doses	↓	↓	Tablets: 50 mg, 100 mg, 150 mg, 300 mg
venlafaxine IR	75 mg/day in 2 or 3 doses	150 mg/day in 2 or 3 doses	375 mg/day in 3 doses	↓	↓	Tablets: 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg
venlafaxine ER (Effexor XR)	37.5 to 75 mg once daily	75 mg to 225 mg once daily	225 mg once daily	↓	↓	ER capsules: 37.5 mg, 75 mg, 150 mg
venlafaxine ER (Venlafaxine ER)	37.5 to 75 mg once daily	75 mg to 225 mg once daily	225 mg once daily	↓	↓	ER tablets: 37.5 mg, 75 mg, 150 mg, 225 mg
vilazodone HCl (Viibryd)	10 mg once daily for 7 days, then 20 mg once daily for 7 days; may be increased to 40 mg/day after a minimum of 7 days between dosage increases	20 mg to 40 mg once daily	40 mg once daily	--	--	Tablets: 10 mg, 20 mg, 40 mg Starter Pack: seven 10 mg and twenty-three 20 mg tablets (30 tablets/pack)
vortioxetine (Trintellix)	10 mg once daily	20 mg once daily, 5 mg once daily if intolerance	20 mg once daily	--	--	Tablets: 5 mg, 10 mg, 20 mg

Doses are FDA-approved doses for outpatients.
-- = no dosage change required; ↓ = consideration should be given to reducing the dose and/or dosage frequency;
nr = not reported

Although desvenlafaxine dosages greater than 50 mg/day were shown to be effective in clinical trials (50 to 400 mg/day), no additional benefit was demonstrated. Adverse events and discontinuations were, however, more frequent with dosages exceeding 50 mg/day.

In elderly patients with GAD, duloxetine (Cymbalta, Drizalma Sprinkle) should be initiated at a dose of 30 mg once daily for 2 weeks prior to considering increasing the dose to a target of 60 mg/day. In children and adolescents 7 to 17 years of age with GAD, initiate duloxetine (Cymbalta, Drizalma Sprinkle) at a dose of 30 mg once daily for 2 weeks prior to considering an increase to 60 mg/day; the recommended dose in this population is 30 mg to 60 mg per day. Drizalma Sprinkle capsules may be swallowed whole or opened and sprinkled over applesauce or administered via a nasogastric (NG) tube; do not check or crush these capsules. Cymbalta capsules must be swallowed whole.

To minimize the risk of seizures, bupropion dose increases should not exceed 100 mg/day in a 3-day period and the maximum daily dosage of 450 mg (522 mg of bupropion HBr) should not be exceeded. Increases above 300 mg/day (348 mg/day of bupropion HBr) should only be used in patients with no clinical effects after several weeks of treatment at 300 mg/day. The time between doses should be at least 4 hours for 100 mg IR doses, 6 hours for 150 mg IR doses, and 8 hours for SR doses. Cautious dose titration can also minimize agitation, motor restlessness, and insomnia. Bupropion HBr ER should be administered once daily as a single-dose. Bupropion ER (Forfivo XL) is available only as an extended-release 450 mg tablet. Therapy should not be initiated with the 450 mg dose, rather titration with other bupropion formulations should be utilized to achieve desired doses.

Venlafaxine has an ascending dose-response curve.[252] At the starting dosage of 75 mg/day, venlafaxine produces approximately the same number of responders as do the SSRIs. The percentage of responders increases with higher doses in a manner consistent with the drug's dual mechanism of inhibiting the uptake of serotonin initially and then norepinephrine at higher doses. Consistent with its pharmacology, higher doses of venlafaxine can also cause a higher incidence of serotonin- and norepinephrine-mediated adverse effects, including the potential to increase blood pressure.

The recommended dosing for esketamine (Spravato) for treatment-resistant depression (TRD) is separated into induction and maintenance phases. Dosage adjustments for TRD should be made based upon efficacy and tolerability, and therapeutic benefit should be carefully evaluated after the induction phase to determine the need for further treatment. For acute suicidal thoughts or behaviors, a lower dose of 56 mg twice weekly may be considered for tolerability reasons. Following 4 weeks of treatment for this indication, treatment should be reevaluated, as treatment beyond 4 weeks has not been evaluated. Blood pressure, for all indications, must be assessed prior to and following administration, as described in the Warnings section above. If blood pressure is elevated (> 140/90 mmHg), consider the benefits versus the risk of administration; esketamine should not be administered if an increase in blood pressure or intracranial pressure poses a serious risk. For all administrations, patients should be educated to avoid food for ≥ 2 hours before the dose and to avoid drinking liquids ≥ 30 minutes prior to dose in order to reduce nausea and vomiting associated with esketamine. Patients should not drive or operate machinery until the day after administration, following a restful sleep; the patient will require transportation following administration. For all indications, esketamine (Spravato) should be administered in conjunction with an oral antidepressant. Full administration information is outlines in the product labeling.

Levomilnacipran (Fetzima) should not be taken with alcohol because alcohol affects the extended-release properties of the product and a pronounced accelerated drug release may occur.

Vilazodone (Viibryd) should be taken with food because administration without food reduces bioavailability and inadequate drug concentrations may result.

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A gradual reduction in the dose of SNRIs rather than abrupt cessation is recommended whenever possible.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Fibromyalgia and diabetic peripheral neuropathic pain are not included in this review. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Studies of less than 6 weeks duration were excluded since this short timeframe may be insufficient to appropriately evaluate the effects of antidepressant agents. Smaller studies of MDD (fewer than 100 patients) were not included in this evaluation. Due to the high loss of patients in psychotropic studies during follow-up, trials with more than 20% loss were still considered for inclusion in this review. Studies focusing specifically on the elderly population or on inpatients were excluded because they are not applicable to the patient population under consideration. Studies that did not use the standard rating scales described below were also excluded. Likewise, rigorous clinical trials of select older agents within this class are limited (e.g., isocarboxazid [Marplan]).

Efficacy Scales

The 2 most common methods of reporting the efficacy results of antidepressant clinical trials are response rates and remission rates. Response is defined as a 50% reduction in severity of the depressive syndrome as measured by a standardized scale or a rating of much or very much improved as assessed by a global assessment method. Remission is a full resolution of the depressive syndrome such that the patient scores in the non-depressed range on such a standardized scale. In clinical trials of antidepressants, the percentage of patients who remit on placebo usually ranges from 20% to 30% while the remission rate on active drug is generally 45 to 60%. In most studies, response rates are 10% to 15% higher than the remission rate.

For MDD, 2 of the most commonly used standardized rating scales are the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS).

HAM-D – This scale is used to assess the severity of MDD in patients already diagnosed with an affective disorder. It is the most widely used and accepted outcome measure for evaluating depression severity. The HAM-D is the standard depression outcome measure used in clinical trials presented to the FDA by pharmaceutical companies for approval of New Drug Applications. The standard HAM-D-21 contains 21 questions. The more commonly used HAM-D-17 excludes 4 questions relating to diurnal variation, depersonalization and derealization, paranoid symptoms, and obsessional and compulsive

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symptoms. The remaining 17 questions are related to symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels, and weight loss.[253] The HAM-D-17 provides ratings on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision.

MADRS – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness.[254]

Other standardized scales used in the evaluation of the drugs in this class include:

HAM-A (Hamilton Anxiety Rating Scale) – This is the most frequently used and accepted outcome measure for the evaluation of anxiety in clinical trials. The HAM-A consists of 14 items, each defined by a series of symptoms such as anxiety, tension, depressed mood, palpitations, breathing difficulties, sleep disturbances, restlessness, and other physical symptoms.[255] It is included in the National Institute of Mental Health's Early Clinical Drug Evaluation Program Assessment Manual, designed to provide a standard battery of assessments for use in psychotropic drug evaluation.

CGI-I (Clinical Global Impression – Improvement) – This 3-item scale assesses the patient's improvement or worsening.[256]

CGI-S (Clinical Global Impression – Severity) – This 3-item scale assesses the clinician's impression of the current state of the patient's illness. The rater is asked to consider his total clinical experience with the given population.[257]

PGI (Patient Global Impression – Improvement) – Patients use this scale to rate his or her own improvement.

VAS (Visual Analog Scale) – This is 1 of the most frequently used measurement scales in healthcare research, most commonly used for the measurement of pain.[258,259,260] This scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli.

LSAS (Liebowitz Social Anxiety Scale) – This is a questionnaire whose objective is to assess the range of social interaction and performance situations those individuals with social phobia may fear and/or avoid. It is also a popular measurement tool used by researchers to evaluate the efficiency of various social anxiety disorder treatments, including pharmacological trials. A modified social anxiety scale exists for children and adolescents.

SPIN (Social Phobia Inventory) – This self-assessment consists of questions that evaluate fear, avoidance, and physiological discomfort.[261]

BPI (Brief Pain Inventory) – This questionnaire provides information on the intensity of pain (sensory dimension), as well as the degree to which pain interferes with function (reactive dimension). The BPI also asks questions about pain relief, pain quality, and the patient's perception of the cause of pain.

QIDS-C$_{16}$ (16-Item Quick Inventory of Depressive Symptomatology-Clinician Rated questionnaire) – This 16 item questionnaire classifies the severity of depression.[262]

QLDS (Quality of Life in Depression Scale) – This is a 34-item, depression-specific, health-related quality of life instrument that assesses the ability and capacity of individuals to satisfy their daily needs.[263,264]

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Q-LES-Q (Quality of Life Enjoyment and Satisfaction Questionnaire) – This is a self-report measure designed to enable investigators to easily obtain sensitive measures of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning.[265]

SDS (Sheehan Disability Scale) – A self-rated, 3-item rating scale used to measure the degree of disease-related disability in the domains of work, family, and social relationships. The limitation of this disability rating scale is that some patients may not accurately recognize their degree of disability until after successful treatment.[266]

PAAS (Panic and Anticipatory Anxiety Scale) – A rating scale for treatment efficacy assessment obtained from a daily diary maintained by the study participant and used to measure the number of panic attacks experienced, the number of episodes of anticipatory anxiety, and the percentage of time in each 24-hour period spent worrying about having a panic attack (anticipatory anxiety).[267]

CDRS-R (Children's Depression Rating Scale-Revised) – Modeled after the HAM-D, the CDRS-R is a clinical interview tool designed for assessing children 6 to 12 years of age, and it has also been used successfully for adolescents. The CDRS-R helps clinicians rate 17 symptom areas: impaired schoolwork, difficulty having fun, social withdrawal, appetite disturbance, sleep disturbance, excessive fatigue, physical complaints, irritability, excessive guilt, low self-esteem, depressed feelings, morbid ideas, suicidal ideas, excessive weeping, depressed facial affect, listless speech, and hypoactivity. It is used to diagnose depression and can be repeated to measure response to treatments.[268]

Major Depressive Disorder

bupropion (Aplenzin)

There are no clinical trials available meeting criteria that demonstrate the effectiveness of this bupropion formulation.

bupropion IR versus fluoxetine (Prozac®)

Patients with MDD were, after a 1-week placebo phase, randomly assigned to receive bupropion IR 225 to 450 mg/day or fluoxetine 20 to 80 mg/day for 6 weeks in a double-blind study.[269] The mean daily dose at the end of this 123 patient study was 382 mg for bupropion IR and 38 mg for fluoxetine. There were no statistically significant differences between treatments on any of the efficacy variables. Response, based on HAM-D, occurred in 63% of bupropion treated patients and 58% of fluoxetine-treated patients (p=NS [not significant]). Response based on CGI scores occurred in 68% and 58% of patients, respectively (p=NS). HAM-A improved by 59% for both treatment groups. There were no significant differences in the improvements in CGI-S and CGI-I. The incidence of treatment-emergent adverse events was low with no statistically significant differences between treatments. The manufacturer of bupropion IR funded the study.

bupropion IR versus trazodone

After a 1-week placebo lead-in, 124 outpatients with moderate to severe MDD were randomly assigned, in double-blind fashion, to receive bupropion IR 225 mg to 450 mg per day or trazodone 150 mg to 400 mg per day for 6 weeks.[270] Data from the 111 patients used in the efficacy analysis showed that the overall efficacy for each of the 2 drugs was similar. Improvement in the trazodone treatment group was significantly greater on day 7 because of its effect on sleep. At the end of treatment, 58% of bupropion-treated patients and 46% of trazodone-treated patients were CGI responders. This is

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equivalent to an odds ratio (OR) for bupropion versus trazodone of 1.38 / 0.82 = 1.62 indicating that, based on this study, the odds are 62% better for achieving clinical response with bupropion compared with trazodone.[271] Anorexia and anxiety were reported significantly more often for the bupropion group. Somnolence, appetite increase, and edema were reported significantly more often in the trazodone group.

bupropion versus SSRIs (sertraline [Zoloft®], paroxetine [Paxil®], and escitalopram [Lexapro®])

Six double-blind, randomized clinical trials comparing bupropion (n=662) with an SSRI (n=655) for the treatment of MDD were pooled to examine whether the treatment of MDD with bupropion results in a greater resolution of sleepiness and fatigue than with the SSRIs: sertraline, paroxetine, or escitalopram.[272] Among the 6 studies pooled, 3 studies used sertraline, 1 used paroxetine, and 2 used escitalopram as the SSRI comparator. Hypersomnia scores were defined as the sum of scores of the Hamilton Depression Rating Scale (HDRS) items #22, 23, and 24. Fatigue scores were defined as the score of HDRS item #13. There was a greater improvement in hypersomnia scores among bupropion-treated than SSRI-treated ($p < 0.0001$) or placebo-treated patients ($p = 0.0008$). There was also a greater improvement in fatigue scores among bupropion-treated ($p < 0.0001$) and SSRI-treated ($p = 0.0005$) than placebo-treated patients, as well as a greater improvement in fatigue scores among bupropion-treated than SSRI-treated patients ($p = 0.0078$). Fewer bupropion-remitters than SSRI-remitters experienced residual hypersomnia (20.5% versus 32.1%; $p = 0.0014$) or residual fatigue (19.5% versus 30.2%; $p = 0.0020$). The manufacturer of bupropion sponsored the study.

bupropion XL (Wellbutrin XL) versus escitalopram (Lexapro)

In 2 identical, double-blind, controlled-trials, 830 patients with MDD were randomized to receive bupropion XL 300 mg to 450 mg, escitalopram 10 mg to 20 mg, or placebo once daily for up to 8 weeks.[273] Pooled data showed a significant difference between escitalopram and placebo, but not bupropion XL and placebo, in HAM-D-17 total scores. There were no significant differences among active treatments with respect to mean change in HAM-D-17, HAM-D-17 response or remission rates, percentage of patients much or very much improved on CGI-I, or change in CGI-S.

bupropion XL (Forfivo XL)

There are no separate, independent clinical trials available meeting criteria to establish the efficacy of the extended-release 450 mg formulation of bupropion.[274] Efficacy in the treatment of MDD was determined from previous trials of the immediate-release formulation of bupropion, as well as data demonstrating bioequivalence of this specific formulation to other extended-release bupropion formulations.

desvenlafaxine base versus placebo

The approval of the base formulation of desvenlafaxine was based on the short-term pivotal clinical trials conducted comparing placebo to the succinate salt; no additional clinical studies were conducted.[275]

desvenlafaxine succinate (Pristiq) versus placebo

Desvenlafaxine succinate was evaluated in four, 8-week, randomized, double-blind, placebo-controlled, fixed-dose studies in adult patients with MDD. Doses studied ranged from 50 mg/day to 400 mg/day. Desvenlafaxine succinate was superior to placebo in improvement in the HAM-D-17 total score (primary endpoint) in all 4 studies and in the CGI-I in 3 of the 4 trials.[276,277,278,279,280]

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Longer-term efficacy was established in 2 maintenance trials.[281] One study evaluated the longer-term efficacy of desvenlafaxine succinate 50 mg/day using a withdrawal design. Adult patients with MDD and a HAM-D-17 total score ≥ 20 (n=548) at baseline who responded to 8 weeks of open-label treatment with desvenlafaxine 50 mg/day and had sustained response through week 20 were randomized to placebo or continued desvenlafaxine succinate in a 6-month, double-blind, randomized withdrawal period.[282] The primary endpoint, time to relapse (HAM-D-17 total score ≥ 16, discontinuation for unsatisfactory response, hospitalization for depression, suicide attempt, or suicide) was significantly shorter in the placebo group (p<0.001). At 6 months, the probability of relapse was 30.2% in the placebo group compared to 14.3% for the desvenlafaxine succinate group. A second similarly designed study evaluated adult patients with MDD who responded to therapy on desvenlafaxine succinate 200 mg/day or 400 mg/day (defined as a HAM-D-17 total score ≥ 11 at day 84).[283] Patients were randomized to continue on their same dosage or switch to placebo for up to 26 weeks. At week 26, the probability of relapse was 29% in the desvenlafaxine succinate group compared with 49% in the placebo group.

duloxetine (Cymbalta) versus placebo with escitalopram (Lexapro) as an active comparator

A randomized, double-blind, placebo- and active comparator-controlled study included patients 18 years of age and older meeting DSM-IV criteria for MDD. Patients received duloxetine 60 mg once daily (n=273), escitalopram 10 mg once daily (n=274), or placebo (n=137).[284] The 8-week study was conducted to compare the speed of onset of antidepressant efficacy for duloxetine and escitalopram and to test whether duloxetine was at least as effective as escitalopram. Onset of efficacy was defined as a 20% decrease from baseline on the HAM-D-17 Maier subscale at week 2 that was maintained or exceeded at all subsequent visits. In this study, both duloxetine and escitalopram showed significantly greater improvement on the primary efficacy measure than placebo over the 8-week acute treatment period, while no differences were observed between drugs or between drugs and placebo on response and remission rates at 8 weeks. Escitalopram at a starting dose of 10 mg daily was better tolerated than duloxetine at a starting dose of 60 mg daily as noted by more frequent occurrence of nausea, dry mouth, vomiting, yawning, and irritability for duloxetine-treated patients. This study's pre-defined primary objective was met and showed that duloxetine is not inferior to escitalopram in terms of onset of efficacy.

esketamine (Spravato) versus placebo

TRANSFORM-2, a phase 3, multicenter, randomized, placebo-controlled, double-blind study assessed the efficacy and safety of esketamine for treatment-resistance depression (TRD).[285,286] TRANSFORM-2 included patients 18 to 64 years of age with a DSM-5 diagnosis of single-episode (duration ≥ 2 years) or recurrent MDD, without psychotic features who were considered treatment resistant. Exclusion criteria included previous nonresponse to esketamine or ketamine in the current episode or to all 4 of the oral treatment options available for the double-blind induction phase (duloxetine, escitalopram, sertraline, and venlafaxine XR). There was a 4-week prospective screening and observational phase in which patients continued the same oral antidepressants. Then, there was a 4-week, randomized, double-blinded, placebo-controlled phase. Patients entered in this phase must have had non-response (defined as ≤ 25% improvement) to ≥ 2 different antidepressant agents prescribed in adequate dosages for an adequate duration, with non-response to 1 antidepressant having been demonstrated in the prospective, observational phase. Then, the 227 eligible patients were randomized to receive either esketamine or placebo nasal spray twice weekly, each combined with 1 of 4 choices of newly initiated, open-label antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine). Dosing in this study

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was flexible (56 mg or 84 mg) and patients could be titrated up to 84 mg starting with the second dose, based on investigator discretion. The primary efficacy measure was change from baseline in the MADRS total score at the end of the 4 weeks. The esketamine (56 mg to 84 mg) group demonstrated statistical superiority from baseline to day 28 in mean MADRS total score compared to the placebo group of -19.8 versus -15.8, respectively (least squares mean difference, -4; 95% CI, -7.31 to -0.64; p=0.02).

SUSTAIN-1, a phase 3, randomized, treatment-withdrawal trial, assessed relapse prevention. Adults 18 to < 65 years of age who were known remitters and responders were enrolled from either previous nasal esketamine trials (with efficacy) or direct entry patients who met the same inclusion and screening criteria as patients in previous esketamine trials. [287,288] For the direct enrolled patients, there was a 4-week induction period during which patients received twice weekly esketamine (56 mg or 84 mg) plus newly initiated oral antidepressant. This was followed by a 12-week optimization phase for responders, during which patients continued with the same dose of esketamine plus antidepressant at less frequent esketamine dosing (weekly for 4 weeks, then based on symptoms, changed to weekly or every other week). This was then followed by a 48-week maintenance phase. In the maintenance phase, patients who were stable remitters (MADRS total score ≤ 12 for ≥ 3 of the last 4 weeks) or stable responders (≥ 50% MADRS total score reduction for ≥ 3 of the last 4 weeks but not in remission) were separately randomized to continue with esketamine or switch to placebo nasal spray (in addition to the oral antidepressant). The primary study endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRS total score ≥ 22 for 2 consecutive weeks, hospitalization for worsening depression, or any other clinically relevant event indicative of relapse. The median time to relapse was not estimable for the esketamine plus antidepressant group, as the 50% relapse rate was not reached based on Kaplan-Meier estimates. A longer time to relapse of depressive symptoms occurred in stable *remitters* treated with esketamine than with placebo (estimated hazard ratio [HR], 0.49; 95% CI, 0.29 to 0.84). A longer time to relapse of depressive symptoms also occurred in stable *responders* treated with esketamine than with placebo (estimated HR, 0.3; 95% CI, 0.16 to 0.55) using Cox proportional hazards.

Two, 4-week, phase 3, multicenter, double-blind, randomized, placebo controlled trials (ASPIRE I [n=226] and II [n=226]) established the efficacy of esketamine for the treatment of adults with moderate to severe MDD (MADRS total score > 28) with active suicidal ideation and intent.[289,290,291] In both studies, all patients received comprehensive standard of care treatment, which included initial inpatient hospitalization and a newly initiated or optimized antidepressant (e.g., antidepressant, antidepressant plus augmentation therapy; determined by investigator). Patients were randomized to either esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks. Following the first dose, a 1-time dose reduction to 56 mg esketamine was permitted due to poor tolerability in those assigned active treatment. The mean patient age across both trials was 40 years (range, 18 to 64), and 61% were female, 73% were Caucasian, and 63% had at least 1 prior attempt. In addition, 40% received background antidepressant monotherapy, 54% received antidepressant plus augmentation therapy, and 6% received a combination of monotherapy and antidepressant augmentation therapy during the course of the study. The primary endpoint was the change from baseline in total MADRS at 24 hours (on day 2) following the first dose. The LS mean difference in MADRS at this time period, favoring treatment, was -3.8 (95% CI, -6.56 to -1.09) in ASPIRE I and -3.9 (95% CI, -6.6 to -1.11) in ASPIRE II. Treatment difference was observed beginning at 4 hours following the initial dose. The change in CGI of Suicidal Severity – Revised (CGI-SS-r) score at the same time point was also assessed, but not statistical difference was found between groups.

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levomilnacipran (Fetzima) versus placebo

Levomilnacipran, 40 to 120 mg once daily, was studied in three, 8-week placebo-controlled studies; 2 were fixed-dose trials and 1 was a flexible-dose trial. There was no active comparator used in these studies. Adult outpatients with a diagnosis of MDD were enrolled.[292,293,294] In all 3 trials, all doses of levomilnacipran were superior to placebo in improvement of depressive symptoms measured by the MADRS total score at 8 weeks. Levomilnacipran was superior to placebo in improvement in the key secondary endpoint, the Sheehan Disability Scale (SDS) for most dosages examined.

A maintenance study of levomilnacipran demonstrated its efficacy compared to placebo for the treatment of MDD in a double-blind, treatment-withdrawal clinical trial.[295] Patients received flexibly dosed levomilnacipran (range, 40 mg to 120 mg) for 8 weeks. Those with a response were then eligible to enter a 12-week open-label stabilization phase. Those stabilized with continued response (based on MADRS ≤ 12) then entered the 26-week treatment-withdrawal study. Notably, approximately half of the participants were receiving doses of 120 mg/day. The primary endpoint was relapse, defined as MADRS ≥ 18 at 2 consecutive visits, or insufficient response as defined by the investigator. Those assigned to continue levomilnacipran demonstrated a greater time to the primary endpoint based on Kaplan-Meier estimates.

mirtazapine (Remeron) versus paroxetine (Paxil)

A total of 197 patients with MDD were randomized to 24 weeks of therapy with mirtazapine 30 to 45 mg/day or paroxetine 20 to 30 mg/day in a double-blind manner.[296] Both treatments were efficacious in improving depressive symptomatology, as assessed by group mean HAM-D-17, percentages of HAM-D responders and remitters, and CGI responders. The mirtazapine group showed statistically significantly larger decreases from baseline in the group mean HAM-D-17 at weeks 1, 2, and 4. Statistically significant decreases with paroxetine were seen at weeks 2 and 4. Mirtazapine had a significantly higher incidence of fatigue while paroxetine had significantly more patients complaining of increased sweating, headache, and nausea.

mirtazapine (Remeron SolTab) versus sertraline (Zoloft)

In a double-blind, multicenter study, 345 patients with MDD were randomized to receive mirtazapine orally dissolving tablets 30 mg/day to 45 mg/day or sertraline 50 mg/day to 150 mg/day for 8 weeks.[297] The primary efficacy variable, the mean change from baseline in the HAM-D-17, showed that mirtazapine was significantly (p<0.05) more effective than sertraline at all assessments during the first 2 weeks of the study. After this time, the HAM-D-17 was similar in both groups. Reduction in sleep disturbance was significantly greater in the mirtazapine group (p≤0.01). Both drugs also yielded similar effects in terms of HAM-D response, HAM-D remission rate, MADRS, and CGI. Approximately two-thirds of the patients in each treatment group reported at least 1 adverse event; 13% of patients in the mirtazapine group and 3% of the sertraline group withdrew from the study due to adverse events.

nefazodone versus placebo

A total of 165 outpatients with chronic MDD were enrolled in a randomized trial comparing nefazodone (maximum dose 600 mg/day) and placebo.[298] During the 1-year study of maintenance treatment, the occurrence of major depressive episodes was assessed with the HAM-D and a blinded review of symptom exacerbations. At the end of 1 year, the probability of recurrence was 30.3% for nefazodone-treated patients and 47.5% for patients receiving placebo (p=0.043). Somnolence was

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significantly greater among the patients taking active medication (15.4%) compared with placebo (4.6%).

phenelzine (Nardil) versus tranylcypromine (Parnate)

Phenelzine and tranylcypromine were compared in a double-blind, flexible dose study with 77 severely depressed patients with treatment-resistant depression.[299] Patients had previously been treated with tricyclic antidepressants or fluvoxamine. A total of 87% of patients completed the trial with 52% of patients responding to therapy. Response was defined as a ≥ 50% reduction in HAM-D scores. No significant differences in response between both drugs were observed. Seventeen (44%) of 39 patients responded to tranylcypromine, and 18 (47%) of 38 responded to phenelzine. The mean reduction in HAM-D score was 10.4 +/- 8.3 for the tranylcypromine sample versus 8.3 +/- 8.4 for the phenelzine-treated patients. Only 10% of patients used concomitant psychotropic medication. The most common adverse effects were dizziness, agitation, and insomnia; the incidence was the same in both groups (21%).

selegiline (Emsam) versus placebo

Following a 1-week placebo lead-in, 177 adults with MDD were randomly assigned to receive selegiline 6 mg/24 hours or placebo transdermally in a double-blind manner for 6 weeks.[300] At the conclusion of the trial, patients in the selegiline group showed significantly greater improvement than placebo in HAM-D-17 (p=0.01), MADRS (p=0.005), and CGI-S (p=0.007). Most responders showed improvement after 1 week of treatment. Five percent of patients in each group withdrew from the study due to adverse events. Application site reactions occurred in 36% of patients receiving selegiline and 17% of those receiving placebo (p=0.006).

In a double-blind study, 289 adults with MDD were randomized to receive selegiline 6 mg/24 hour or placebo transdermal patches daily for up to 8 weeks.[301] Selegiline was superior to placebo on the MADRS (p=0.001), but not on the HAM-D-17 or CGI-S. Side effects were similar in the 2 groups, with the exception of application site reaction, which occurred in 32% of the selegiline-treated patients and 15% of placebo-treated patients (p=0.001).

In a similar study, 265 patients with MDD were randomized, in double-blind fashion, to receive selegiline 6 mg/24 hour or placebo transdermal patches for 8 weeks.[302] Doses could be increased per protocol for patients who failed to show therapeutic response. At the conclusion of the study, selegiline was superior to placebo as measured by the HAM-D-28 and MADRS (p≤0.05 for both endpoints).

In a 52-week, double-blind, placebo-substitution, parallel-group clinical trial, safety and efficacy of initial and continuation selegiline in patients with MDD were assessed.[303] After 10 weeks of treatment with selegiline transdermal 6 mg/24 hr, 322 patients who responded with a HAM-D-17 score of 10 or less were randomly assigned to double-blind treatment with selegiline transdermal 6 mg/24 hr or placebo for 52 weeks. At study week 52, significantly fewer selegiline patients experienced relapse of MDD episode (n= 25/149 [16.8%]) compared with placebo (50/163 [30.7%]; p=0.0025). Additionally, patients receiving selegiline transdermal experienced a significantly longer time to relapse compared with those receiving placebo (p=0.0048). The safety profile of selegiline transdermal was similar to placebo, with the exception of application-site reactions.

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trazodone versus fluoxetine (Prozac)

Outpatients with current nonpsychotic major depressive episodes of at least 4 weeks duration were given single-blind placebo for 1 week, after which they were randomized to double-blind treatment with fluoxetine or trazodone for 6 weeks.[304] The median sustained doses in the 126 patients in the study were 250 mg/day for trazodone and 20 mg/day for fluoxetine. The HAM-D-21 improved similarly in both treatment groups (p<0.001 for each group compared to baseline). There were no differences between the groups in CGI-S, CGI-I, or PGI-I. More fluoxetine-treated patients reported rhinitis and tremor (p≤0.05), and more trazodone-treated patients reported somnolence and dizziness (p≤0.05). More combined events suggesting activation (agitation, anxiety, nervousness, insomnia) were reported with fluoxetine (15.4%) than with trazodone (3.3%, p≤0.05). More combined events suggesting sedation (somnolence, asthenia) were reported with trazodone (42.6%) than with fluoxetine (21.5%, p≤0.05). Discontinuation rates for activation and sedation did not differ between treatments. The manufacturer of fluoxetine conducted the study.

venlafaxine IR versus fluoxetine (Prozac)

In an 8-week, multicenter, double-blind, parallel-group study, 382 outpatients with moderate to severe MDD for at least 1 month were randomized to treatment with venlafaxine IR 37.5 mg twice daily or fluoxetine 20 mg once daily.[305] Daily doses could be doubled after 3 weeks for poor response. Both drugs produced significant improvements from baseline in mean HAM-D and MADRS (p<0.05), but no significant differences were noted between groups. High response rates were noted with 81% in the venlafaxine group and 84% in the fluoxetine group achieving that endpoint. Remission was observed in 60% of the patients in each group. There were no significant differences in the occurrence of adverse events between groups. The manufacturer of venlafaxine IR funded the study.

In an 8-week double-blind study, 314 patients with MDD were randomized to venlafaxine 37.5 mg twice daily or fluoxetine 20 mg once daily.[306] If the response was inadequate after 2 weeks of treatment, the dosage of venlafaxine could be increased to 75 mg twice daily. Both treatment groups significantly improved HAM-D, MADRS, and CGI from baseline. While the HAM-D response at week 6 was higher in the venlafaxine group (72%) than the fluoxetine group (60%; p=0.023), there was no significant difference at the conclusion of the study. Significantly more patients reported nausea in the venlafaxine group (28 versus 14%; p=0.003). The rate of withdrawal from the study due to adverse events was 9% in the venlafaxine group and 4% in the fluoxetine group.

In a multicenter, double-blind study, 341 patients with MDD and symptoms for more than 2 weeks were randomized to venlafaxine 75 mg/day or fluoxetine 20 mg/day, each given as fixed doses for 12 weeks.[307] Both treatments significantly improved MADRS, HAM-D-21, and CGI; there were no significant differences between groups. Response was noted in 55% of venlafaxine patients and 63% of fluoxetine patients. Remission occurred in approximately 35% of patients in each group. These low active-treatment remission rates are likely due to the use of a more conservative definition of remission (MADRS ≤ 6 rather than the more usual ≤ 10). There were no significant differences in adverse events between groups.

venlafaxine IR versus sertraline (Zoloft)

In a multicenter, double-blind study, 147 patients with MDD were randomized to receive venlafaxine IR 37.5 mg twice daily or sertraline 50 mg once daily for 8 weeks.[308] After 2 weeks, the doses could be increased to venlafaxine IR 75 mg twice daily or sertraline 50 mg twice daily. There were no significant

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differences between treatments in mean changes in HAM-D-21, MADRS, or CGI-I, although each improved significantly from baseline. At the conclusion of the study, the HAM-D-21 response rate was higher in the venlafaxine IR group (83%) than in the sertraline group (68%; p=0.05). Similarly, HAM-D-21 remission rates were higher in the venlafaxine IR group than in the sertraline group (68% and 45%, respectively; p=0.008); this difference was more pronounced in patients who increased the dose. There were no significant differences observed between treatment groups for adverse events. The manufacturer of venlafaxine IR funded the study.

venlafaxine IR versus venlafaxine ER (Effexor XR)

In a double-blind study, 287 patients with MDD were randomized to receive venlafaxine IR 37.5 mg twice daily, venlafaxine ER 75 mg once daily, or placebo for a maximum of 12 weeks.[309] If the response was inadequate after 2 weeks of treatment, the daily dose of venlafaxine could be increased to 150 mg. Both dosage forms of venlafaxine were significantly superior to placebo beginning at week 2 for the HAM-D and at week 3 for the MADRS. Significant improvement in CGI-S began at week 6 for venlafaxine IR and at week 4 for venlafaxine ER. Venlafaxine ER exhibited superiority over venlafaxine IR at week 12 for all efficacy variables.

venlafaxine ER (Effexor XR) versus escitalopram (Lexapro)

An 8-week, randomized, double-blind study compared the efficacy and tolerability of escitalopram to venlafaxine ER in 293 primary care patients with MDD.[310] The efficacy of escitalopram 10 mg to 20 mg was similar to venlafaxine ER 75 mg to 150 mg, based on mean change from baseline to week 8 in MADRS. Response rates were 80% in the venlafaxine ER group and 77% in the escitalopram group (p=NS). Remission rates were 70% in each group, although sustained remission was attained nearly 1 week earlier in the escitalopram group compared to the venlafaxine ER group. More venlafaxine ER-treated patients had nausea, constipation, and increased sweating than patients treated with escitalopram (p<0.05 for each comparison). When treatment was completed after 8 weeks, significantly more venlafaxine ER-treated patients had discontinuation symptoms (p<0.01).

In a randomized trial, 195 outpatients with MDD received 1 week of single-blind placebo treatment, followed by 8 weeks of double-blind, fixed-dose treatment with either escitalopram or venlafaxine ER, rapidly titrated to 20 mg/day and 225 mg/day, respectively.[311] Mean changes from baseline to endpoint in MADRS for escitalopram and venlafaxine ER were similar. Response rates for the escitalopram and venlafaxine ER groups were 59% and 48%, respectively (p=NS). Remission rates at endpoint were 41% for escitalopram and 37% for venlafaxine ER (p=NS). The venlafaxine ER group had a higher incidence of treatment-emergent adverse events (85%) and discontinuation due to adverse events (16%) than the escitalopram group (68% and 4%, respectively; p<0.05 for both comparisons).

venlafaxine ER (Effexor XR) versus fluoxetine (Prozac)

In a multicenter, double-blind study, 301 patients with MDD were randomized to venlafaxine ER 75 mg/day to 225 mg/day, fluoxetine 20 mg/day to 60 mg/day, or placebo; doses could be increased after 2 weeks.[312] At the 8-week endpoint, there were no significant differences between the 2 active treatments on HAM-D-21 or MADRS in the LOCF analysis. Both active treatments significantly improved HAM-D-21 compared to placebo. Only venlafaxine ER improved MADRS and CGI compared to placebo. Venlafaxine ER patients experienced significantly more dizziness and nausea than fluoxetine or placebo patients (p<0.05). The manufacturer of venlafaxine ER funded the study.

venlafaxine ER (Effexor XR) versus sertraline (Zoloft)

In an 8-week double-blind study, 163 subjects with MDD were randomized to receive venlafaxine ER 75 mg/day to 225 mg/day or sertraline 50 mg/day to 150 mg/day.[313] There were no significant differences in the effects of the 2 agents on Q-LES-Q (the primary endpoint), HAM-D, HAM-A, or CGI-S. The lack of difference was also noted for 2 predetermined subgroups – patients with anxious depression and those with severe depression. Withdrawal due to adverse events occurred in 8.4% of venlafaxine ER patients and 3.8% of sertraline patients. The manufacturer of sertraline funded this study.

vilazodone HCl (Viibryd) versus placebo

The safety and efficacy of vilazodone as a treatment for MDD were established in 4, multicenter, randomized, double-blind, placebo-controlled trials in outpatient adults (ages 18 to 70 years) with MDD. Three studies were 8 weeks in duration, while the fourth was 10 weeks. In all studies, patients were randomized to vilazodone (20 mg or 40 mg; 40 mg was target dose in the first 3 trials) or to placebo once daily with food. Patients assigned to 20 mg and 40 mg were titrated to the goal dose over 1 week and 2 weeks, respectively. The primary endpoint in all trials was depression improvement as measured by the change in MADRS at the end of the study period. CGI-S was also evaluated in 2 of the 4 studies. In the first 8-week study, Study 1, the placebo-subtracted difference in MADRS total score in the 40 mg vilazodone group was -3.2 (95% CI, -5.2 to -1.3).[314] In Study 2 and Study 3, the placebo-subtracted difference in MADRS total score in the 40 mg vilazodone group were -2.5 (95% CI, -4.4 to -0.6) and -5.1 (95% CI, -6.9 to -3.3), respectively.[315,316] In the 10-week study, Study 4, the placebo-subtracted difference in MADRS total score was -2.6 (95% CI, -4.3 to -0.8) and -2.8 (95% CI, -4.6 to -1.1) in the 20 mg and 40 mg vilazodone groups, respectively.[317] Citalopram was also included in this trial as an active comparator and resulted in a placebo-subtracted difference in MADRS total score of -2.7 (95% CI, -4.5 to -1). Significant differences also were seen in both vilazodone groups and in the citalopram group when compared to placebo in CGI-S total score (p<0.01 for all groups).

vortioxetine (Trintellix) versus placebo

Vortioxetine was evaluated in 6 short-term, 6- to 8-week randomized, double-blind, placebo-controlled, fixed-dose studies in patients with MDD.[318,319] Five were conducted in adults 18 to 75 years of age and 1 in adults aged 64 to 88 years of age (Study 6). The dosage of vortioxetine varied among studies from 5 mg/day to 20 mg/day with those randomized to 15 mg/day or 20 mg/day being titrated up from an initiation dosage of 10 mg/day. In each of the first 6 studies, at least 1 vortioxetine dosage group was superior to placebo in change from baseline in the HAMD-24 or MADRS and each dosage group was superior to placebo in at least 1 study. Studies conducted in the US (3 of the first 6 studies; Studies 4, 5, and 6) showed that the 20 mg/day dosage was the most effective; lower doses were generally not consistently efficacious in US studies, but were shown to be effective in studies conducted outside the US. Efficacy was typically observed starting at week 2 with full antidepressant effects observed after week 4. In Study 1, the placebo-subtracted differences in MADRS at study end were -5.9 (95% CI, -8.6 to -3.2) and -5.7 (95% CI, -8.5 to -2.9) in the vortioxetine 5 mg/day and 10 mg/day groups, respectively.[320] In Study 2, the placebo-subtracted differences in HAMD-24 at study end were -4.1 (95% CI, -6.2 to -2.1) and -4.9 (95% CI, -7 to -2.9) in the vortioxetine 5 mg/day and 10 mg/day groups, respectively.[321] In Study 3, the placebo-subtracted differences in MADRS at study end were -5.5 (95% CI, -7.7 to -3.4) and -7.1 (95% CI, -9.2 to -5) in the vortioxetine 15 mg/day and 20 mg/day groups, respectively.[322] In Study 4, the placebo-subtracted differences in MADRS at study end were -1.5 (95% CI, -3.9 to 0.9; not significant [NS]) and -2.8 (95% CI, -5.1 to -0.4) in the vortioxetine 15

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mg/day and 20 mg/day groups, respectively.[323] In Study 5, the placebo-subtracted differences in MADRS at study end were -2.2 (95% CI, -4.5 to 0.1; NS) and -3.6 (95% CI, -5.9 to -1.4) in the vortioxetine 10 mg/day and 20 mg/day groups, respectively.[324] In Study 6, the elderly population, the placebo-subtracted difference in HAMD-24 at study end was -3.3 (95% CI, -5.3 to -1.3) in the vortioxetine 5 mg/day group.[325]

In 2 additional studies, Studies 7 and 8, patients were evaluated with the Digit Symbol Substitution Test (DSST) to assess processing speed and cognitive function while taking vortioxetine compared to placebo.[326] In Study 7, the placebo-subtracted differences in DSST at study end were 4.2 (95% CI, 2.5 to 5.9) and 4.3 (95% CI, 2.6 to 5.9) in the vortioxetine 10 mg/day and 20 mg/day groups, respectively. In Study 8, the placebo-subtracted differences in DSST at study end were 1.8 (95% CI, 0.3 to 3.2) in the group receiving a flexible dose of vortioxetine 10 mg or 20 mg daily.

In a non-US maintenance study, Study 9, patients meeting DSM-IV-TR criteria for MDD received flexibly dosed vortioxetine (5 mg or 10 mg) daily during a 12-week open-label phase[327] Patients were then randomized to continue their final response dose or to placebo for 24 to 64 weeks. Patients assigned to continue treatment had a longer time to recurrence compared to patients assigned placebo (treatment discontinuation) (p-value not provided).

Generalized Anxiety Disorder (GAD)

duloxetine (Cymbalta) versus placebo

Three independent clinical studies were randomized, double-blind, placebo-controlled multicenter studies which were conducted in adult outpatients with DSM-IV-defined GAD. The studies examined the efficacy of duloxetine treatment for improving functional outcomes for patients with GAD.[328] One study compared 9-week, fixed-dose treatment with duloxetine 60 mg or 120 mg (n=168 and n=170, respectively) with placebo (n=175). The other 2 studies compared 10-week, flexible-dose treatment with duloxetine 60 mg to 120 mg (study 2, n=168; study 3, n=162) with placebo (study 2, n=159; study 3, n=161). The main functional outcome measure for each study was the Sheehan Disability Scale (SDS). Duloxetine-treated patients improved significantly more than placebo-treated patients on SDS global functioning (study 1, p≤0.001; studies 2 and 3, p≤0.01) and SDS work, social life, and family/home responsibilities scores (p value range, ≤0.05 to ≤0.001). At treatment endpoint, a greater percentage of duloxetine-treated patients had obtained SDS global functioning scores in the normative range than placebo-treated patients (p value range, ≤0.05 to ≤0.001). Duloxetine-treated patients also reported greater increases in quality of life, well-being, and health compared with the placebo group on the other functional measures (p value range, ≤0.05 to ≤0.001).

In a 10-week, double-blind, flexible-dose trial, 327 adult outpatients with GAD were randomized to duloxetine 60 mg to 120 mg (n=168) or placebo (n=159) treatment for the evaluation of efficacy, safety, and tolerability of duloxetine in the treatment of GAD.[329] The primary efficacy parameter was mean change from baseline to endpoint HAM-A total score. Patients who received duloxetine demonstrated significantly greater improvement in HAM-A total scores (p=0.02); a higher response rate (p=0.03), and greater improvement (p=0.04) than patients who received placebo. Duloxetine-treated patients were also significantly more improved than placebo-treated patients on SDS global functional (p<0.01) and work, social, and family/home impairment scores (p<0.05). Discontinuation rate for adverse effects was higher for the duloxetine group compared with the placebo group (p=0.002). The most common adverse effects with duloxetine were nausea, dizziness, and somnolence.

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venlafaxine ER (Effexor XR) versus placebo

In a double-blind study, 251 non-depressed outpatients with GAD requiring treatment were randomly assigned to receive either venlafaxine ER or placebo for 28 weeks.[330] The dosage of venlafaxine ER (75, 150 or 225 mg/day) was based on symptom response. During weeks 6 through 28, response rates in the venlafaxine ER group were at least 69% compared with 42% to 46% in the placebo group (p<0.001). By an evaluable-patient analysis, venlafaxine ER significantly improved all primary efficacy measures from week 1 or 2 through week 28, including the HAM-A, CGI-I, and CGI-S (p<0.001 for all comparisons to placebo). The most common treatment-emergent adverse event was nausea, followed by somnolence and dry mouth.

In 5 multicenter, double-blind, clinical trials, 1,839 adult outpatients with GAD were randomized to receive fixed or flexible doses of venlafaxine ER 37.5 to 225 mg/day or placebo.[331] Three trials were 8 weeks in duration; 2 trials were 24 weeks in duration. For the CGI-I, 66% of patients aged 60 years or older responded to venlafaxine ER compared to 41% of patients on placebo (p<0.01). For patients less than 60 years of age, comparable figures were 67% and 44%, respectively (p<0.001). In older adults, 23% of venlafaxine ER patients and 31% of placebo patients discontinued treatment prematurely; comparable figures for younger adult patients were 27% for the venlafaxine ER group and 28% for the placebo group, respectively. Discontinuations due to adverse events were 15% and 14% for venlafaxine ER and placebo, respectively, in older adults compared with 15% and 8% for younger adults.

In a 24-week, double-blind, parallel-group study, 244 primary care patients with GAD were randomized to receive venlafaxine ER 75 mg or placebo, each given daily.[332] After 2 weeks, the dose could be doubled if the physician considered the response poor. At 24 weeks, the HAM-A showed improvement in the venlafaxine ER group (p=0.05 compared to placebo). Remission rates measured at 24 weeks were 28% for the venlafaxine ER group and 19% for the placebo group (p=0.11).

Social Anxiety Disorder

venlafaxine ER (Effexor XR) versus placebo

A multicenter, double-blind trial examined the efficacy and safety of venlafaxine ER in the treatment generalized social anxiety disorder.[333] A total of 272 outpatients were randomly assigned to receive either flexible dose venlafaxine ER 75 mg to 225 mg per day or placebo for 12 weeks. Venlafaxine ER was significantly more effective than placebo as demonstrated by the LSAS at weeks 4 to 12. Both the CGI-S and CGI-I showed that venlafaxine ER was significantly more effective than placebo at weeks 4 to 12. Response rates were significantly higher in the venlafaxine ER group throughout the last 8 weeks of the study. The FDA-approved dosage of venlafaxine ER for social anxiety disorder is 75 mg per day.

In a multicenter study, 386 outpatients with social anxiety disorder were randomized to venlafaxine ER 75 mg per day fixed-dose, venlafaxine ER 150 mg to 225 mg per day flexible dose, or placebo.[334] In the double-blind study, improvement on the LSAS, the primary outcome, was greater with either regimen of venlafaxine ER than placebo. This improvement was sustained throughout the 6-month trial. Of patients receiving either dose of venlafaxine ER, 58% responded to treatment compared to 33% of those receiving placebo (p<0.001). Corresponding remission rates were 31% and 16%, respectively (p<0.01). There were no differences in outcome between the 2 venlafaxine ER dosage regimens. The FDA-approved dosage of venlafaxine ER for social anxiety disorder is 75 mg/day.

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venlafaxine ER (Effexor XR) versus paroxetine (Paxil)

A total of 434 adult outpatients with social anxiety disorder were randomized to receive venlafaxine ER 75 mg to 225 mg per day, paroxetine 20 mg to 50 mg per day, or placebo in a double-blind manner for 12 weeks.[335] Patients with other anxiety or depressive disorders were excluded from the trial. Treatment with venlafaxine ER or paroxetine was associated with significantly greater improvement in LSAS (primary efficacy variable), CGI-I, and SPIN than treatment with placebo (p<0.05 for all comparisons to placebo). No significant differences in any of the efficacy variables were observed between the venlafaxine ER and paroxetine groups. The week 12 response rates were similar for the venlafaxine ER (69%) and paroxetine (66%) groups and were significantly higher than the placebo group (36%; p<0.05). Both active treatments were generally well tolerated and were associated with a similar incidence of adverse events. The FDA-approved dosage of venlafaxine ER for social anxiety disorder is 75 mg per day. The manufacturer of venlafaxine ER funded the study.

Panic Disorder

venlafaxine ER (Effexor XR) versus placebo

In a double-blind trial, 361 adults with panic disorder were randomized to receive venlafaxine ER 75 mg to 225 mg per day or placebo for up to 10 weeks.[336] In the study, there was no difference between treatment groups in the proportion of patients free from full-symptom panic attacks (≥ 4 symptoms), although there were fewer limited-symptom panic attacks in the venlafaxine ER group. Venlafaxine ER was also associated with a lower mean frequency of panic attacks, as well as higher response and remission rates and improvements in anticipatory anxiety, fear, and avoidance.

venlafaxine ER (Effexor XR) versus paroxetine (Paxil)

A total of 664 non-depressed adult outpatients who met DSM-IV criteria for panic disorder (with or without agoraphobia) were randomly assigned to 12 weeks of treatment with placebo or fixed-dose venlafaxine ER 75 mg or 150 mg per day, or paroxetine 40 mg per day in a double-blind study in the treatment of panic disorder.[337] The primary measure was the percentage of patients free from full-symptom panic attacks, assessed with the Panic and Anticipatory Anxiety Scale (PAAS). Secondary measures included the Panic Disorder Severity Scale, CGI-S, and CGI-I scales; response (CGI-I rating of very much improved or much improved), remission (CGI-S rating of not at all ill or borderline ill and no PAAS full-symptom panic attacks); and measures of depression, anxiety, phobic fear and avoidance, anticipatory anxiety, functioning, and quality of life. Intent to treat, last observation carried forward analysis showed that mean improvement on most measures was greater with venlafaxine ER or paroxetine than with placebo. No significant differences were observed between active treatment groups. Panic-free rates at endpoint with active treatment ranged from 54% to 61%, compared with 35% for placebo. Approximately 75% of patients given active treatment were responders, and nearly 45% achieved remission. The placebo response rate was slightly above 55%, with remission near 25%. Adverse events were similar for active treatment groups and mild to moderate.

Seasonal Affective Disorder

bupropion ER (Wellbutrin XL) versus placebo

The efficacy and safety of bupropion ER to prevent major depressive episodes associated with seasonal affective disorder were established in 3, randomized, placebo-controlled, trials in the US and Canada (n=1,042).[338] Adults with seasonal affective disorder who were enrolled in autumn and currently well

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were randomized to either bupropion ER 300 mg (following a 1 week 150 mg/day titration period) or placebo daily through spring and then followed for an additional 8 weeks following medication discontinuation. The primary outcomes were end-of-treatment depression-free rates and depression recurrence as determined by survival analysis. Recurrence rates were 19% with bupropion ER and 30% with placebo in study 1 (p=0.026), 13% with bupropion ER and 21% with placebo in study 2 (p=0.049), and 16% with bupropion ER and 31% with placebo in study 3 (p<0.001) (pooled relative risk reduction, 44%). Kaplan-Meier survival analysis of depression recurrence also favored bupropion ER over placebo (p=0.081, p=0.057, and p<0.001 in study 1, 2, and 3, respectively).

META-ANALYSES

Depression

One systematic review indicated that, based on fair-to-good evidence, the second generation antidepressants all have similar efficacy in treating MDD.[339] Of 46 randomized, controlled trials directly comparing agents in this class, all but 5 reported no statistically significant difference in any outcome measure at the end of the study. Meta-analyses suggest a small, but statistically significant, additional treatment effect for sertraline and venlafaxine compared with fluoxetine.

In another systematic review, researchers analyzed the results of 81 clinical trials involving more than 10,000 adults with MDD that compared newer antidepressants with placebo.[340] Mirtazapine, venlafaxine, nefazodone, and bupropion were among the drugs included in this review, as were several SSRIs. As a group, the newer antidepressants were significantly (60%) more effective than placebo. The efficacy of different antidepressant classes was similar, as were the individual agents in each class. A comparison of older antidepressants with newer agents found no significant difference in efficacy with the exception of 3 studies showing a 20% greater effect for an SNRI than for trazodone (p=0.05).

A different systematic review of 39 placebo-controlled randomized controlled trials of duloxetine, venlafaxine, and the SSRI, fluoxetine, used meta-regression analysis to compare the relative treatment effect of duloxetine with venlafaxine and fluoxetine in patients with MDD.[341] This analysis found no significant difference in treatment effect, as measured by HAM-D, between duloxetine and fluoxetine. It did, however, identify significantly better efficacy of venlafaxine compared to duloxetine with an OR of 2 for the number of responders.

A network meta-analysis compared the efficacy (defined as partial response; a 50% reduction in depression score from baseline) and safety of sertraline, venlafaxine, citalopram, paroxetine, duloxetine, fluoxetine, and escitalopram in adults ≥ 60 years (15 RCTs; n=4,588).[342] Only 3 agents demonstrated statistically significant efficacy over placebo in partial response: sertraline (relative risk [RR], 1.28; 95% CI, 1.07 to 1.51), paroxetine (RR, 1.48; 95% CI, 1.27 to 1.75), and duloxetine (RR, 1.62; 95% CI, 1.26 to 2.05). Compared to placebo, dizziness was statistically higher with venlafaxine (RR, 3.18; 95% CI, 1.6 to 6.03) and duloxetine (RR, 2.94; 95% CI, 1.03 to 8.37). Data on falls, syncope, and vertigo were too few to provide reliable conclusions.

The TORDIA (Treatment of Resistant Depression in Adolescents) study was a National Institute of Mental Health-sponsored, 12-week, double-blind, randomized, controlled trial of 334 patients aged 12 to 18 years with a primary diagnosis of MDD that had not responded to a 2-month initial treatment with an SSRI.[343] The patients were randomized to 1 of 4 groups: (1) switching to a second, different SSRI (paroxetine, citalopram, or fluoxetine, 20 mg to 40 mg), (2) switching to venlafaxine ER (150 mg to 225 mg), (3) switching to an alternative SSRI and receiving cognitive behavioral therapy (CBT), or

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(4) switching to venlafaxine ER and receiving CBT. The primary outcome measures were Clinical Global Impressions-Improvement (CGI-I) score of ≤ 2 (much or very much improved); a decrease of at least 50% in the Children's Depression Rating Scale-Revised (CDRS-R); and change in CDRS-R over time. CBT plus a switch to either medication regimen showed a higher response rate (54.8%; 95% CI, 47% to 62%) than a medication switch alone (40.5%; 95% CI, 33% to 48%; p=0.009), but there was no difference in response rate between venlafaxine ER and a second SSRI (48.2%; 95% CI, 41% to 56% versus 47%; 95% CI, 40% to 55%; p=0.83). There were no differential treatment effects on change in the CDRS-R, self-rated depressive symptoms, suicidal ideation, or on the rate of harm-related or any other adverse events. There was a greater increase in diastolic blood pressure and pulse and more frequent occurrence of skin problems during venlafaxine ER than SSRI treatment. For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of CBT and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone. However, a switch to another SSRI was just as efficacious as a switch to venlafaxine ER and resulted in fewer adverse effects.

A network meta-analysis comparing the efficacy and tolerability of antidepressants for MDD in children and adolescents found limited information demonstrating no clear advantage of one agent over another (34 trials; n=5,260).[344] Antidepressants assessed included mirtazapine, fluoxetine, nortriptyline, paroxetine, clomipramine, nefazodone, venlafaxine, escitalopram, citalopram, imipramine, desipramine, amitriptyline, and sertraline. The only treatment that was better than placebo was fluoxetine (Standard mean difference [SMD], -0.51; 95% CI, -0.99 to -0.03). Likewise, nortriptyline was significantly less effective than multiple other antidepressants and placebo. Fluoxetine was also better tolerated than duloxetine and imipramine, while citalopram and paroxetine were better tolerate than imipramine. The authors concluded fluoxetine may be the best option when treatment is indication although data for a clear advantage was limited. Few published data for each drug and potential confounders within the methodology of a network meta-analysis limit these results.

Another network meta-analysis compared the efficacy of antidepressants, psychotherapies, and their use in combination for the acute treatment of children and adolescents with major depressive disorder.[345] Head-to-head and placebo-controlled trials of antidepressants, various psychotherapies, and 5 combinations were included (71 trials; n=9,510). Regarding notable findings of agents included that are also in this class (desvenlafaxine, duloxetine, mirtazapine, nefazodone, venlafaxine, vilazodone), none were statistically superior to placebo in efficacy or all-cause discontinuation.

A Bayesian meta-analysis was conducted to compare the evidence of efficacy for second-generation antidepressants in the treatment of depression using phase 2 or phase 3 data.[346] Only antidepressant data from the 134 clinical trials that used FDA-approved doses were included for bupropion, citalopram, escitalopram, fluoxetine, paroxetine, paroxetine controlled-release, sertraline, duloxetine, mirtazapine, nefazodone, venlafaxine, venlafaxine extended-release, levomilnacipran, desvenlafaxine, vortioxetine, and vilazodone. The strongest evidence load for efficacy was found for levomilnacipran, desvenlafaxine, and duloxetine; the lowest evidence load for efficacy was found with vilazodone. All antidepressants were found to have at least "strong evidence" for their efficacy with the exception of bupropion and vilazodone. Venlafaxine, followed by paroxetine and venlafaxine extended-release, had the highest estimated effect size. Desvenlafaxine had the highest estimated certainty for the effect size, followed by levomilnacipran. The authors concluded that this type of analysis may be used by providers to select venlafaxine to treat depression due to its top ranking in the combined evidence load and effect size compared to the other antidepressants reviewed. Additional patient specific

clinical considerations are necessary for drug selection; however, this type of Bayesian analysis may assist prescribers by differentiating the level of evidence found in efficacy studies.

A systematic review and meta-analysis assessed the optimal dose of SSRIs (excluding fluvoxamine), venlafaxine, and mirtazapine in the acute treatment of adults with MDD (77 studies; n=19,364).[347] Doses of SSRIs were assessed in fluoxetine equivalents. The authors assessed treatment response (≥ 50% reduction in target symptoms), dropouts secondary to adverse effects, and all-cause dropouts after a median of 8 weeks of treatment. For the SSRIs, there was a dose response at all doses; however, there was a gradual increase from 20 mg to 40 mg fluoxetine equivalents followed by flat to decreasing trends at higher approved fluoxetine equivalent doses. Venlafaxine was found to have an increasing dose-efficacy relationship up to doses of 150 mg, followed by a more slow increase in dose-efficacy at higher doses. Mirtazapine was found to have dose-efficacy response up to 30 mg, followed by a decrease in dose-efficacy response at higher doses. There was a dose-dependent increase in dropouts for all medications due to adverse events.

Other Indications

A Cochrane review evaluated the safety and efficacy of second generation antidepressants for the treatment of seasonal affective disorder compared to placebo or other interventions, such as light therapy or psychological therapies (3 RCTs; n=1,100).[348] Only studies evaluating the efficacy of bupropion XL (Wellbutrin XL) met inclusion criteria. Results suggest bupropion XL is efficacious (risk ratio [RR], 0.56; 95% CI, 0.44 to 0.72; number needed to treat [NNT] based on yearly recurrence, 8 [95% CI, 6 to 12]) when compared to placebo. However, the findings also suggest that the risk of headache, insomnia, and nausea were higher with bupropion XL compared to placebo.

One meta-analysis examined the risk of relapse and time to relapse in patients who responded to antidepressant medications for anxiety disorders (e.g., post-traumatic stress disorder [PTSD], obsessive compulsive disorder [OCD], generalized anxiety disorder [GAD], phobias).[349] All studies included in the analysis randomized participants to either continue antidepressant therapy or switch to placebo. Results suggest that treatment discontinuation (via placebo) is more likely to result in relapse than continuing antidepressant therapy (28 RCTs; n=5,233; odds ratio [OR], 3.11; 95% CI, 2.48 to 3.89). Additionally, discontinuation of therapy was found to have a shorter relapse time (11 RCTs; n=3,002; hazard ratio [HR], 3.63; 95% CI, 2.58 to 5.1). Overall, this data suggests that those with anxiety disorders may benefit from chronic treatment.

A systematic review and network meta-analysis evaluated efficacy of pharmacological treatments for GAD compared to placebo (89 trials, n=25,441).[350] Among the agents within this therapeutic class, duloxetine (mean difference, -3.13; 95% CI, -4.13 to -2.13) and venlafaxine (mean difference, -2.69; 95% CI, -3.5 to -1.89) were found to be effective when compared to placebo in mean change in HAM-A from baseline and did not favor placebo in overall adverse effect profile. Findings for mirtazapine and buspirone appear superior to placebo in efficacy but were limited by small sample sizes. Notably, several included trials were not completed in the US; however, this is the largest, most recent network meta-analysis of these agents for GAD.

SUMMARY

All second generation antidepressants have demonstrated effectiveness at reducing symptoms of depression; there are no significant differences in efficacy among these agents across the general population. This is borne out in data from individual clinical trials, as well as from systematic reviews;

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however, little comparative data are available on newer agents, such as esketamine (Spravato), vilazodone (Viibryd), vortioxetine (Trintellix), or levomilnacipran (Fetzima). It should be noted that some products have additional indications beyond MDD and anxiety disorders. In addition, each agent has its own pharmacologic profile, which may contribute to improved efficacy or tolerability in patients on an individualized level.

All of the antidepressants in this class have a boxed warning regarding suicidality in children, adolescents, and young adults through the age of 24 years. Related risks as compared to benefits of therapy in this population continue to be evaluated, but data appears to indicate a greater benefit than risk as long as providers, families, and caregivers are aware of and mitigate the risks. Use caution in prescribing these agents, and observe patients for signs of these and other adverse effects.

Notably, these products have different adverse effect profiles. As efficacy is generally comparable among agents across a population, treatment selection often depends on adverse effect profiles, drug interactions, patient history, and other patient-specific considerations. SSRIs are generally accepted as having mild adverse events overall. Adverse events reported with vilazodone appear to be similar to those reported with the SSRIs, but nausea has been reported in clinical trials. SNRIs may be as effective as SSRIs, but have some differing adverse events. Venlafaxine (venlafaxine IR, Effexor XR, Venlafaxine ER, generic) is associated with higher rates of nausea and vomiting than select SSRIs. Venlafaxine and desvenlafaxine are also associated with a higher rate of discontinuation syndrome than other second generation antidepressants. In placebo-controlled trials, discontinuation of duloxetine (Cymbalta, Drizalma Sprinkle) has occurred as a result of higher rates of nausea, vomiting, dizziness, somnolence, and fatigue. Initiation of vortioxetine (Trintellix) is associated with high rates of nausea, but this appears to dissipate after a median of 2 weeks on therapy. For other agents, bupropion (Wellbutrin SR/XL, Forfivo XL, generic) appears to have the lowest risk of sexual adverse effects, although reports are variable. Mirtazapine (Remeron, Remeron SolTab) is associated with weight gain, while bupropion results in a net loss of body weight. Mirtazapine, nefazodone, and trazodone are more likely to cause sedation, but this may be of benefit in patients with depression-related insomnia. Selegiline transdermal (Emsam) is associated with relatively few systemic effects, but it is associated with a high rate of skin reactions and dietary restrictions at certain doses.

Esketamine (Spravato), an intranasally administered product, is approved for use in treatment-resistant depression and is the only agent approved in this class specifically for depressive symptoms with acute suicidal ideation or behavior. For approval for acute suicidal thoughts or behaviors, its use was studied in combination with initial inpatient hospitalization and comprehensive standard of care treatment, including a newly initiated or optimized antidepressant (e.g., antidepressant, antidepressant plus augmentation therapy). For treatment-resistant depression, although there are various treatment options, these are limited by wide patient variability and limited robust outcome data; esketamine has not been addressed in treatment guidelines. Use of esketamine requires a Risk Evaluation and Mitigation Strategies (REMS) program to limit and monitor adverse effects (e.g., dissociation, sedation). Additionally, esketamine can affect blood pressure. Other logistical considerations may affect those eligible for treatment (e.g., REMS enrolled healthcare facility, appropriate blood pressure monitoring, transportation). Esketamine is a Schedule III controlled substance.

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219 Nardil [package insert]. New York, NY; Pfizer; August 2018.

220 Emsam [package insert]. Morgantown, WV; Mylan; May 2020.

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